DISEASES of the CHEST

VOLUME 40 AUGUST, 1961 NUMBER 2

The Suprarenal Function in Allergic Asthma

Determination of the Plasma and Urinary 17-OH-Corticoids and of the Urinary 17-Ketosteroids Before and After ACTH Zn.*

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Introduction

The connection between suprarenal function and allergic diseases has been the subject of some investigation. In 1922, Kenipow found that anaphylactic reactions were increased in guinea pigs whose suprarenal glands had been partially removed. Later Eriksson-Lihr *et al.*[5] found that the daily excretion of the 17-ketosteroids was decreased in allergic diseases; these observations were subsequently confirmed by other authors. Rose and his colleagues[11] have studied the daily excretion of the 17-OH-corticoids in patients during the dyspneic crisis and they have found it decreased. Siegel *et al.*[13] have determined 17-OH-corticoids of the plasma in asthmatic patients and they have found increased values, particularly in patients with intense symptoms.

In previous works,[16,17] we have studied the blood proteins and electrolytes in 40 patients with respiratory allergy, most of them asthmatic. We found a decrease of sodium and plasma chlorine and an increase of potassium and globular chlorine; these variations were highly significant from the point of view of statistics and they were similar to those observable in suprarenal insufficiency. Subsequently we have carried out[19] with the same type of patients the determination of the urinary 17-ketosteroids and the eosinophil counts before and 24 hours after intramuscular injection of 80 units of ACTH gel. We found initially low values of 17-ketosteroids and a highly significant decrease (P=0.001) of the response to the ACTH. These findings have led us to a thorough study of the suprarenal function in allergic asthma.[20]

Material and Methods

The intramuscular ACTH Zn test, according to the original method of Jenkins *et al.*,[9] was done on 22 adults, 11 women and 11 men, whose asthma was of definite allergic origin. A total of 40 units of slow-acting corticotrophine was administered.

Urine specimens were carefully collected 24 hours before and after the administration of ACTH and the plasma 17-OH-korticoids were determined according to the technique of Saier *et al.*,[12] the urinary 17-OH-corticoids by the method of Silber and Porter[14] and the urinary 17-ketosteroids by the method of Cahen and Salter.[2]

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The patients were previously studied from the allergic point of view by means of skin tests; most of them were shown to be sensitive to house dust and to fungi.

The patients were examined clinically before and after the administration of corticotrophine in order to appraise the intensity of symptoms and they were classed in three groups: (1) asymptomatic patients, seven cases; (2) patients with slight symptoms (nasal obstruction, faint sibilant rales), ten cases; (3) patients with intense symptoms (subjective dyspnea, abundant sibilant rales, and increased respiratory frequency), five cases.

In order to avoid all disturbing influence on the test, patients were chosen who *had never taken corticoids.*

In order to suppress hourly variations in the level of the plasma 17-OH-corticoids, all the blood counts were taken at the same time, that is at 8 a.m., the moment when the corticoids reach their highest level; this is the time at which most authors made determinations.

Results

Urinary 17-ketosteroids: The excretion of the 17-ketosteroids 24 hours before administration of ACTH showed decreased values. The average obtained in men was 9.6 standard deviation ±2.8 mg./24h. and in women, 7.1 standard deviation ± 2.8 mg./24h.; these are low values compared with those given by de Gennes,[7] in whose Department the determinations were carried out, and who considers as normal values for a male adult from 8 to 22 mg. per day with an average of 14 mg./24h. and for women from 5 to 15 mg./24h. with an average of 9 mg./24h. On their part, Cahen and Salter,[2] authors of the chemical method used, also gave figures

TABLE 1—VALUES OF PLASMA AND URINARY CORTICOIDS OBTAINED IN MALE PATIENTS WITH RESPIRATORY ALLERGIES

		Before ACTH				After ACTH				
Men	Age	17-CT Urinary mg./24h.	17-OH Urinary mg./24h.	17-OH Plasma μg. per cent	Symptomatology	17-CT Urinary mg./24h.	17-OH Urinary mg./24h.	17-OH Plasma 8h.aft.	17-OH Plasma 24h.aft.	Symptomatology
F.A.	33	12.4	3.9		S.S.	14.2	9.4			S.S.
F.E.	51	10.0	5.7	9	I.S.	9.0	20.6		19	S.S.
H. M.	51	15.7	5.2	6	S.S.	12.3	10.5	7	10	S. S.
CH.E.	58	10.1	8.2	32	S.S.	10.8	30.3		37	W.S.
C.R.	52	9.2	8.5	15	I.S.	8.5	11.7	25		S.S.
G.L.	55	5.5	4.5	27	W.S.	3.7	5.1			W.S.
M.R.	46	9.9	6.6	34	W.S.	11.2	8.3		26	W.S.
A.R.	54	6.5	7.1	23	W.S.	8.1	8.2		25	W.S.
L.M.	19	10.8	2.7	14	S.S.	5.4	3.5		17	S.S.
F.J.	18	9.6	5.5	27	S.S.	12.0	8.5		29	S.S.
S.A.	51	6.8	5.2		I.S.	11.2	14.3			I.S.
Average	44	9.6	5.1	20.7		9.6 +0%	11.4 +123%		23.2	
Standard Deviation		±2.8	±1.7	±10.4		±3.2	±7.7		±10.1	
Standard Error		±0.9	±0.5	± 3.7		±1.0	±2.4		± 4.2	

References: W.S.=without symptoms; S.S.=slight symptoms; I.S.=intense symptoms.

higher than those we found in asthmatic patients; they give from 13 to 19 mg./24h. for normal men and from 9 to 16 mg./24h. for women.

More important than the low elimination of the 17-ketosteroids was the absence of response to the administration of ACTH. Indeed, the average values for men were the same after the administration of ACTH; 9.6 standard deviation ± 3.2 mg./24h.; and for women, the rise was very slight: from 7.11 standard deviation ± 2.8 mg./24h. to 8.0 standard deviation ± 2.4 mg./24h., that is to say an average of 12 per cent. De Gennes[7] considers that ACTH raises regularly the proportion of these androgens, twice their value (100 per cent), and that the Thorn test is not normal if the 17-ketosteroids do not reach at least 50 per cent (an average of 5 mg.). Jenkins *et al.*,[8] authors of the method, have observed an average increase of 6 mg. in normal subjects with the intramuscular injection of ACTH gel.

17-Hydroxycorticoids. The urinary elimination of the 17-OH-corticoids before administration of ACTH was an average of 5.1 standard deviation ± 1.7 mg./24h. in men sufferers from respiratory allergies. (Values in normal men: 4 to 8 mg./24h.).[7]

In women the average excretion was from 3.4 standard deviation ± 1.4 mg./24h. (normal values: 2 to 5 mg./24h.). Thus it is clear that the static elimination of 17-OH-corticoids was maintained within normal limits.

The increase induced by the injection of ACTH in men was from 5.1 standard deviation ± 1.7 to 11.4 standard deviation ± 7.7 mg./24h., that is to say of 123 per cent. In women the increase was of 167 per cent, the figures increased from 3.4 standard deviation ± 1.4 to 8.0 standard deviation ± 3.3 mg./24h. De Gennes[7] considers that in normal circumstances the 17-OH-corticoids increase 300 per cent.

One can observe that the basal excretion was normal but that the increase by the action of ACTH was diminished.

TABLE 2—VALUES OF PLASMA AND URINARY CORTICOIDS OBTAINED IN FEMALE PATIENTS WITH RESPIRATORY ALLERGIES

		Before ACTH				After ACTH				
Woman	Age	17-CT Urinary mg./24h.	17-OH Urinary mg./24h.	17-OH Plasma µg. per cent	Symptomatology	17-CT Urinary mg./24h.	17-OH Urinary mg./24h.	17-OH Plasma 8h.aft.	17-OH Plasma 24h.aft.	Symptomatology
L.M.	63	5.8	1.0	9	S.S.	8.2	8.0		11	S.S.
S.M.	41	8.5	3.7	17	S.S.	8.8	11.4	25		W.S.
G.G.	64	4.7	4.3		I.S.	6.6	10.4			I.S.
S.O.	28	8.1	4.2	27	W.S.	9.1	13.7		38	W.S.
H.M.	58	5.2	2.8	41	W.S.	4.3	6.2		31	W.S.
A.M.	54	4.4	3.4	26	S.S.	5.2	4.5		28	S.S.
U.I.	35	11.2	4.9	38	W.S.	13.2	12.1		25	W.S.
P.S.	43	10.1	4.1		W.S.	8.7	5.2			W.S.
L.R.	53	3.9	1.5		S.S.	6.2	6.7			I.S.
D.J.	31	8.1	5.3	24	S.S.	10.4	3.5		17	W.S.
A.L.	40	8.2	3.1	27	I.S.	6.2	6.7			I.S.
Average	46	7.1	3.4	26.1		8.0	8.0		25	
Standard						+12%	+167%			
Deviation		±2.8	±1.4	±9.7		±2.4	±3.3		±9.0	
Standard Error		±0.9	±0.4	±3.4		±0.7	±1.0		±3.7	

References: W.S.=without symptoms; S.S.=slight symptoms; I.S.=intense symptoms.

Plasma 17-hydroxycorticoids. The values of the plasma 17-OH-corticoids found in asthmatic patients at 8 a.m., before injection of ACTH, gave increased values, the average being from 20.7 standard deviation ± 10.4 μg. per cent in men and from 26.1 standard deviation ± 9.7 μg. per cent in women.

Silber and Porter[14] found an average of 13.3 standard deviation ± 6.2 μg. per cent in six normal adults. Eik-Nes *et al.*[4] noted in normal subjects before ACTH, an average of 10 standard deviation ± 3 μg. per cent; two hours after the plasma level rose to 27 sd ± 7 μg. per cent; four hours later to 35 sd ± 10 μg. per cent and after six hours to 40 μg. ± 12 per cent.

On their part, Christy *et al.*[3] found in 11 normal subjects an average of 13 μg. per cent before ACTH and of 44 μg. per cent after ACTH. All these results are noticeably lower than those we have found in our patients.

With regard to the action of ACTH Zn on the plasma levels, we have observed slight variation in the values 24 hours after the intramuscular injection, since a slight increase of 20.7 standard deviation ± 10.4 μg. per cent to 23.2 standard deviation ± 10.1 μg. per cent was noted in men, and in women a slight decrease of 26 standard deviation ± 9.7 μg. per cent to 25 standard deviation ± 9.0 μg. per cent.

We have also carried out on three patients blood counts eight hours after the administration of corticotrophine; in two cases we observed an increase of 17 and 15 μg. per cent to 25 and 25 μg. per cent respectively; in the third case the rise was slight, from 6 μg. per cent to 7 μg. per cent before and after the ACTH.

Even in the two cases where a more marked increase of the plasma 17-OH-corticoids was observed, this increase was lower than that established by Geller *et al.*[6] who found rises of from 15 μg. per cent to 35 μg. per cent, on average, eight hours after the intramuscular injection of ACTH. The same authors have carried out determinations of plasma 17-OH-corticoids every two hours, after intramuscular injection of 40 units of ACTH, in the two forms, Zn and gel.

From the comparative study of the two preparations of corticotrophine they conclude that the highest point is reached two hours after injection of corticotrophine in both forms, while in the gel form it decreases rapidly. On the contrary, with ACTH Zn (which was used in our work) the high level is maintained for up to eight hours, subsequently decreasing progressively. After 24 hours the levels of the plasma corticosteroids are observed to be close to the level before the ACTH.

TABLE 3—COMPARATIVE TABLE OF THE 17-KETOSTEROIDS AND THE 17-OH-CORTICOIDS ACCORDING TO THE SYMPTOMATOLOGY OF PATIENTS

	Before ACTH			After ACTH		
	17-CT Urinary	17-OH Urinary	17-OH Plasma	17-CT Urinary	17-OH Urinary	17-OH Plasma
Patients without Symptoms (7 cases) Average	8.1	4.8	31	8.3	8.4	25
Patients with Slight Symptoms (10 cases) Average	8.9	4.0	19	9.3	9.6	21
Patients with Intense Symptoms (4 cases) Average	7.9	5.4	17	8.0	12.1	23

These authors have shown, in normal subjects, an increase of from two to three times the percentage of the plasma 17-OH-corticoids, after injection of 40 units of ACTH Zn.[8] They conclude that these values eight hours after the administration of slow-acting corticotrophine are the same as those found by Bayliss[1] and Eik-Nes[4] who used the intravenous method, and that the effect produced by 40 units of ACTH Zn is similar to 20 or 25 units of intravenous ACTH.

With regard to the connection between the plasma levels and the intensity of the symptoms, we have observed that asymptomatic patients showed higher plasma levels: 31 μg. per cent on average, and patients with slight and intense symptoms, 19 and 17 μg. per cent, respectively.

Discussion

We shall now consider the state of the suprarenal function in patients suffering from respiratory allergies, with reference to three functions of the suprarenal cortex, the androgenic function, the glycemic function and the mineral function.

The androgenic function was studied by determining the urinary 17-ketosteroids before and after administration of corticotrophine, showing values lower than normal in both sexes. We have arrived at the same results in a previous work[19] carried out on 33 sufferers from respiratory allergy.

The glycemic function was studied by determining the urinary 17-OH-corticoids and by the study of the plasma levels of the glycocorticoids.

The excretion figures of the 17-OH-corticoids were found within normal limits, but the increases after ACTH were lower than 300 per cent; in asthmatic men the increase was 123 per cent and in the women, 167 per cent.

Recently Haydar *et al.*[5] have published seven cases of suprarenal inadequacy with a rise in these, under the action of ACTH, lower than that observed in normal subjects. In these patients, the static 17-ketosteroids were normal, but no rise was produced by the action of the ACTH. The authors consider these as cases of a partial or compensated suprarenal inadequacy. The adrenal function is sufficient for normal needs, but incapable of increasing the secretion of corticosteroids in case of stress or by stimulation with corticotrophine.

Pedersen and Sondergaard[10] have also published a similar case which they called partial Addison's disease with normal excretion of 17-OH-corticoids and absence of response to ACTH by the 17-ketosteroids. De Gennes *et al.*[7] have observed ten similar cases and they have called them subclinical or formes frustes.

Judging from the conclusions of the works quoted above which coincide with the results we have obtained with our patients, it would seem that the androgenic function represented by the 17-ketosteroids is more easily disturbed in cases of subclinical insufficiency than the glycemic function, which maintains the values of 17-OH-corticoids within normal limits.

The high levels of the plasma 17-hydroxycorticoids found in our patients could be explained by the need for hydrocortisone and cortisone to attenuate the allergic reaction present in this type of patient. The antiallergic action of the glycocorticoids is manifested by different mechanisms, by its inhibitory action of the formation of antibodies and probably also by its stimulating action on the cholinesterasic activity, which we have proved in a previous work,[19] and in a symptomatic way by its anti-inflammatory and anti-edema action. However, the glycocorticoids do not exert a direct antihistaminic action. This action explains, in some measure, why patients who show higher plasma levels are precisely those who have no symptoms; on the other hand, in allergic patients studied with both slight and intense symptoms, the plasma levels of the 17-OH-corticoids are lower, thus permitting the appearance of symptoms.

As for the effect of ACTH Zn on the proportion of plasma glycocorticoids 24 hours after intramuscular injection, it has not been perceptibly modified because, as Geller *et al.*[8] have shown, the increase induced by the corticotrophine Zn becomes progressively less pronounced after the eight hours until it reaches levels approximately equal to the initial levels 24 hours after the injection.

In the three cases where determinations of the plasma glycocorticoids were done eight hours after the injection, an absence of response to ACTH was shown in one case, and in the two others a response lower than that found by other authors[4,8] in normal subjects.

With regard to the efficacy of slow-acting ACTH given intramuscularly to stimulate the suprarenal, clinicians[9] have shown that the action of the corticotrophine, both intravenous and intramuscular, produces comparable effects. Geller *et al.*[8] have compared the plasma levels of the 17-OH-corticoids eight hours after stimulation with 40 units of ACTH Zn and they have found them comparable to the plasma levels obtained with 20 to 25 units given intravenously.

The mineral function was indirectly studied in a previous work[16,17] carried out on 40 sufferers from respiratory allergies and we noted a highly significant decrease of sodium and plasma chlorine and an equally significant increase of potassium and globular chlorine, with a decrease of the ratio Na/K as was observed in the suprarenal hypofunction.

These abnormalities could be explained in the following way: the suprarenal of the asthmatic patient, obliged to maintain a high plasma level of glycocorticoids in order to brake the allergic reaction, prefers to produce these hormones to the detriment of the androgenic and mineral function.

Moreover, it is interesting to observe that in allergic patients without symptoms, at the time of the blood determination, we have found the proportion of the plasma 17-hydroxycorticoids comparatively higher than what we have observed in allergic patients with slight and pronounced symptoms. This leads us to think that the stress, in the form of asthma, succeeds not in increasing the plasma glycocorticoids, but on the contrary in decreasing them, probably because the gland has reached the limit of its possibilities of supporting the stress.

Another difficult problem to solve is to know whether the suprarenal hypofunction is primary or secondary to allergy; that is to say, whether the abnormal tendency of certain subjects to acquire diverse sensitizations is due to a congenital dysfunction of the suprarenal gland or if on the contrary the anomalies observed in its function are secondary to the permanent stress represented by the allergic reaction which leads to a progressive weakening of the gland, especially in the androgenic function and probably in the mineral function.

SUMMARY AND CONCLUSIONS

In 22 adult asthmatic patients of definite allergic origin who had never received corticosteroid treatment, the adrenal function was studied by means of the 24-hour test with ACTH Zn given by intramuscular injection. The urinary 17-ketosteroids, the urinary 17-hydroxycorticoids, and the plasma 17-hydroxycorticoids were studied.

Elimination of 17-ketosteroids was found to be diminished before the administration of ACTH. After the ACTH, the increase of the 17-ketosteroids was practically non-existent (+ 6 per cent).

The basal elimination of the 17-hydroxycorticoids was maintained within normal limits. However, the increase after stimulation was less (+ 145 per cent), than that which occurs with normal subjects (+300 per cent).

The proportion of plasma 17-hydroxycorticoids was found higher than the normal proportion. This manifested in inverse ratio to the intensity of symptoms.

The increase of the plasma corticoids eight hours after stimulation with ACTH was found to be diminished.

From these facts it is inferred that in the case of allergic asthma, there is a disturbance which can be classed among the subclinical adrenal insufficiencies, also called partial or compensated adrenal insufficiencies.

ACKNOWLEDGEMENTS: . To Prof. L. de Gennes for having permitted the carrying out of this study in his department; to Profs. J. Turiaf and B. Halpern and Dr. J. Sclafer who gave us the necessary clinical material; to Dr. M. H. Laudat and to Mme. D. Laurent for their technical collaboration.

RESUMEN

Se estudió la función suprarrenal en 22 adultos asmaticos de origen claramente alérgico que nunca habían recibido tratamiento por cortico-esteroides, usando la prueba de las 24 horas con ACTH Zn por vía intramuscular. Fueron estudiados los 17-cetosteroides, urinarios, los 17-hidroxicorcoides urinarios y los 17-hidroxicorticoids en el plasmaticos.

Se encontró que la eliminación de 17 cetosteroides estaba disminuida antes de la administracion del ACTH. Despues del ACTH el aumento de los 17 cetoesteroides practicamente no existía (+ 6 por ciento).

La eliminación basal de los 17 hidroxicorticoides se mantuvo dentro de límites normales. Sin embargo, el aumento después de la estimulación fué menor (+145 por ciento) que el que ocurre en los sujetos normales (+300 por ciento).

La proporción en el plasma de 17-hidroxicorticoides se encontró mas alta que lo normal. Esto se manifestó en razón inversa de la intensidad de los síntomas.

El aumento de los corticoides plasmáticos ocho horas después del estímulo con ACTH, se encontró disminuido.

Se infiere de estos hechos que en el asma alergico hay un trastorno que puede clasificarse entre las insuficiencias suprarrenales subclínicas llamadas también insuficiencias parciales o compensadas de la suprarrenal.

ZUSAMMENFASSUNG

Bei 22 erwachsenen Kranken mit Asthma nachgewiesenen allergischen Ursprungs, die zuvor niemals mit Corticosteroiden behandelt worden waren, wurde die Nebennierenfunktion mittels des 24-Stundentestes mit intramuskulär gegebenem ACTH

geprüft. Untersucht wurden die Urinausscheidungen von 17-Ketosteroiden und 17-Hydroxycorticoiden sowie die Plasmawerte von 17-Hydroxycorticoiden.

Es erwies sich die Ausscheidung von 17-Ketosteroiden herabgesetzt vor der Verabfolgung von ACTH. Nach ACTH war der Anstieg der 17-Ketosteroide praktisch unbedeutend (+ 6%).

Die Basis-Ausscheidung der 17-Hydroxycorticoide blieb innerhalb normaler Grenezn aufrechterhalten. Jedoch betrug die Zunahme nach der Reizung weniger (+145%) als die bei normalen Personen auftretende (+300%).

Der Anteil der 17-Hydroxycorticoide im Plasma lag höher als im Normalfall. Darin kam ein umgekehrtes Verhältnis zur Intensität der Symptome zum Ausdruck. Weiter zeigte sich die Vermehrung der Plasmacorticoide 8 Stunden nach der Reizung mit ACTH herabgesetzt.

Aus diesen Beobachtungen wird der Schluß gezogen, daß im Falle eine allergischen Asthmas eine Störung vorliegt, die eingereiht werden kann unter die klinisch unterschwelligen Nebenniereninsuffizienzen, auch partielle oder kompensierte Nebenniereninsuffizienzen genannt.

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A Controlled Study Using Routine Intermittent Positive Pressure Breathing in the Post-Surgical Patient

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Intermittent positive pressure breathing with oxygen (hereinafter referred to as I.P.P.B.) has rapidly gained wide clinical use in a variety of cardio-pulmonary diseases. Well established as of value in treating some of these patients in the pre- and post-operative state, its "routine" use in the post-operative patient has also been advocated by some as a measure to prevent pulmonary complications.[1,2] The purpose of this controlled study was to evaluate the "routine" use of I.P.P.B. in the patient subjected to upper-abdominal surgery in an effort to clarify its true value in reducing post-operative complications. It was also hoped to determine if I.P.P.B. reduces discomfort and pain by increasing confidence in deep breathing, secondarily affecting ambulation time and total hospital stay.

Method

Because Inter-Community Hospital is a private practice hospital, the cooperation of the doctors was enlisted for the entirety of the study. Only patients who were admitted for upper-abdominal surgery were included in the study irrespective of complications or presence or absence of cardio-pulmonary disease. Every other case on admission was placed in the treatment group and the alternate cases in the controlled group, independent of the specific surgery contemplated. Cases selected were limited to upper-abdominal surgery in order to eliminate the type of surgery as a variable. With this method, 42 cases comprised the treatment group and 42 cases the controlled group. Seventeen cases were dropped, primarily because of lack of cooperation. In a few cases, the private doctor requested that they be dropped from the study because of his desire to use I.P.P.B. on his own in the post-operative period.

On admission to the hospital, each patient was given a pre-operative PA chest roentgenogram, a spirogram, (consisting basically of a maximum breathing capacity, vital capacity, and a three second timed vital capacity), and a cardio-respiratory evaluation by one of the research doctors. An effort was made whenever possible to determine the clinical presence or absence of pulmonary disease pre-operatively. No detailed studies were made, however, other than the history, physical examination spirogram, and chest x-ray film. Patients who reported smoking, but who were asymptomatic and had no pulmonary abnormality on examination, were considered as having no pulmonary disease for study purposes. These data were recorded on a research sheet, which also included age, sex, weight, body build, type of surgery, length of surgery, pre-operative medication, post-operative sedation, ambulation day, and total hospital stay. Each research doctor saw his assigned patients daily, and recorded symptoms, state of comfort, and physical findings. Our department of

TABLE 1—ROENTGENOGRAPHIC COMPLICATIONS IN 84 PATIENTS IN THE POST-OPERATIVE PERIOD

X-ray film change	Treated	Control
Pneumonia or atelectasis (major changes)	6	5
Zonal atelectasis (minor changes)	11	10
No X-ray film change	25	27
Total Cases	42	42

inhalation therapy performed daily vital capacity and three second timed vital capacity tests for five post-operative days. The daily values were expressed as a per cent of their pre-operative recordings taken as 100 per cent. The maximum breathing capacity was impossible to perform in the usual post-operative state. One chest x-ray film was taken on the second or third day post-operatively and again on the fifth day. The x-ray films were taken on the same day on all patients whenever possible. X-ray film evidence of complications was divided arbitrarily into three groups: those with completely normal post-operative x-ray films; those with "minor" x-ray film changes (consisting of platelike atelectasis or apparent uneven aeration); and those with major complications (consisting of pneumonia or atelectasis). The x-ray films were interpreted by two roentgenologists (W. E. Quinn, M.D., and D. Stewart, M.D.) who had no prior knowledge as to which patients were in the treated or in the controlled group.

Treatments

In all cases I.P.P.B. treatments performed by the department of inhalation therapy were started in the recovery room, usually within the first hour post-surgically. Tergemist was used routinely, but no antibiotic or bronchodilator. The latter two were not used as we were dealing basically with healthy individuals without pulmonary disease and the use of these substances would add two more variables difficult to evaluate. Forty per cent oxygen was administered and a pressure of 15 centimeters of water. Treatments were given ten minutes of every hour for three hours; ten minutes of every two hours for the next nine hours; ten minutes of every four hours for the next 12 hours; then four times a day for two more days. In all cases the therapist was in constant attendance during the treatments and urged the patient to make the maximum respiratory

TABLE 2—CORRELATION OF PRE-OPERATIVE CLINIC PULMONARY DISEASE WITH ABNORMAL ROENTGENOGRAPHIC FINDINGS

	Treated Group			Control Group		
C-R Disease	Neg. X-ray	Zonal atelectasis	Pneumonia or atelectasis	Neg. X-ray	Zonal atelectasis	Pneumonia or atelectasis
No Pulmonary Disease	18	7	5	26	6	2
Chronic bronchitis, bronchiectasis, and Smoker's Syndrome	3	3	1	0	1	2
History of Pulmonary disease	4	0	0	1	1	0
Heart Disease	0	1	0	2	1	1

TABLE 3—RELATIONSHIP BODY BUILD AND ABNORMAL ROENTGENOGRAMS

Body Build Type	Abnormal Roentgenograms	
	Treated Group	Control Group
Endomorph	9	9
Mesomorph and Ectomorph	8	6
Total	17	15

effort in both depth and length. This was unsuccessful in many instances due to pain.

Results

Post-operative Roentgenographic Complications (Tables 1 and 2)

The post-operative roentgenogram was the cornerstone of our objective evaluation. Table 1 shows that I.P.P.B. did not prevent post-operative pulmonary complications. Seventeen patients in the treated group were interpreted as having complications, six major (pneumonia or atelectasis) and 11 minor (zonal atelectasis). In the control group, five of the 15 patients had major complications and ten had minor complications.

Table 2 summarizes the relationship between the presence or absence of pre-operative clinical pulmonary or cardiac diseases and post-operative x-ray film changes. The number of patients with pre-operative pulmonary disease was too small to evaluate as a separate group, although pulmonary complications were found in both series irrespective of I.P.P.B. treatments.

Correlation of Abnormal Roentgenograms with other Factors (Table 3)

Body Build

It is well recognized that the elderly obese patient is more prone to have pulmonary complications post-operatively. Review of Table 3 shows that, even though the endomorph has a higher percentage of post-operative complications, I.P.P.B., as used, did not prevent these complications. There were 18 endomorphs in each group studied, nine in each developing post-operative complications. Analyzing only patients with major complications, (Table 9) the endomorph tended again to predominate.

Age and Sex (Tables 4 and 5)

Post-operative pulmonary complications were noted in all age groups. Here again, no significant protection could be attributed to I.P.P.B. treatments in preventing complications in any of these age groups. No correlation was found in this study between the sex of the individual patients, their tendency to develop post-operative complications, or protection from the use of I.P.P.B.

TABLE 4—RELATION BETWEEN AGE AND ABNORMAL ROENTGENOGRAMS

Decade	Treated Group	Control Group
3rd	2	1
4th	4	4
5th	4	5
6th	1	4
7th	3	1
8th	3	0
Total	17	15

TABLE 5
RELATIONSHIP BETWEEN SEX AND ABNORMAL ROENTGENOGRAMS

Sex	Treated Group	Control Group
Female	10	9
Male	7	6

Type of Surgery (Table 6)

Patients having gastric-resections had a higher per cent of complications than those having cholecystectomies and, here again, I.P.P.B. afforded no protection from pulmonary complications.

Spirographic Results (Tables 7 and 8)

A review of the spirographic data demonstrates that I.P.P.B. had no beneficial effect in hastening the return towards normal of the vital capacity. The timed vital capacity data was also comparable in the two groups.

Only a small number of patients had abnormal spirograms pre-operatively. The number is too few to draw any conclusions, although the number of major complications was zero in the treated as compared to two in the control group.

Analysis of Major Complications (Table 9)

Analysis of patients with major complications alone shows no significant variation or difference in the various categories studied as compared to the patients having major and minor complications combined. The overall incidence of major complications was approximately the same in the treated and controlled groups despite the fact that, if anything, more pulmonary disease was present in the treated group.

Miscellaneous Data

No difference in the day ambulated or total days hospitalized was found in comparing the controlled and treated groups.

As an overwhelming number of patients had general anesthesia, this factor was not evaluated. Post-operative analgesics is extremely difficult to evaluate on a comparative basis, but only an occasional patient was found to have "heavy" post-operative sedation, which statistically was not considered significant.

Discussion

I.P.P.B. as used in this control did not prevent post-operative complications even in those few patients with pre-operative pulmonary diseases, abnormal pre-operative spirograms, and the obese. The ability of I.P.P.B. to prevent complications in the post-operative patient, even without cardio-pulmonary disease, would necessarily be based on the following observations: I.P.P.B. increases pulmonary ventilation and tidal

TABLE 6—RELATIONSHIP OF TYPE SURGERY AND ABNORMAL ROENTGENOGRAMS*

Surgery	Number Abnormal	Total Cases
Gastric Resection	9	17
Cholecystectomy	23	67

*Of the four major pulmonary complications in patients with gastric resection, three were in the treated group. Of the eight major complications in those with cholecystectomies, three were in the treated group.

TABLE 7—DAILY AVERAGE SPIROGRAPHIC IMPROVEMENT IN POST-OPERATIVE PERIOD

	Treated Group		Control Group	
Day	V.C.	T.V.C. (3 sec.)	V.C.	T.V.C. (3 sec.)
1st	36 per cent	98 per cent	42 per cent	97 per cent
2nd	48 per cent	97 per cent	53 per cent	94 per cent
3rd	61 per cent	100 per cent	63 per cent	93 per cent
4th	77 per cent	93 per cent	76 per cent	93 per cent
5th	79 per cent	93 per cent	76 per cent	93 per cent
Pre-Op.		89 per cent		91 per cent

volume, increases respiratory depth, causing more uniform alveolar ventilation, and improves bronchial drainage during exhalation because of the high velocity expiratory rate. These effects might be considered generally to maintain ventilation in the post-operative patients, to enhance the elimination of secretions, and thereby to prevent atelectasis.

In trying to explain our negative results, it is possible that the positive pressure used, and the length and depth of each individual respiration was inadequate to produce the desired effects, and that the tidal volume was not increased to the point of therapeutic benefit. This is borne out by the lack of I.P.P.B. to hasten the rate to normal of vital capacity performed in the post-operative period. These findings occurred despite constant urgings by competently trained inhalation therapists to the patients to make maximum respiratory efforts in both depth and length. Each treatment was personally supervised by an inhalation therapist, a condition that would exist in few hospitals today. This emphasizes even more forcibly the danger of leaving the work of stimulating the post-operative patient to breathe to a "machine" even when supervised. Elevating the pressure might help force the issue making it more difficult for the patient to voluntarily stop inspiration. The recognition of these facts compromise the real value of this study. The I.P.P.B. machine, as used in this study, cannot replace the bedside work of the post-operative surgical team.

Further observations bear mention. The research team was unanimous in noting that treated patients complained of "more mucus" than in the control group, and that I.P.P.B. although effective in mobilizing the mucus was not simulating the cough reflex. These patients were actually then unable to raise the loosened secretions, so that retained secretions remained the major problem in both groups. Perhaps use of the coffiator would be a more logical approach to the post-operative patient for this reason.

I.P.P.B. did not seem to reduce post-operative discomfort, did not hasten ambulation time, and did not reduce total hospital stay. These are expected observations when it was shown the post-operative pulmonary complications were not prevented.

Patients treated with I.P.P.B. did not have a more rapid return to normal of the vital capacity in the five day post-operative observation period. This tends to substantiate our impression that with the methods used little improvement was made in overall ventilation.

Nine of 13 "major" complications were not demonstrated clinically during our daily bedside pre-operative examinations. The post-operative patient is, at best, difficult to examine, is loathe to turn, sit up, and to perform deep breathing. These reasons undoubtedly account for the research team's missing the pulmonary abnormalities in such a high percentage of patients. This lends even greater importance to the roentgenogram as being the corner stone of the evaluation of the post-operative patient. This undoubtedly is a frequent occurrence where routine x-ray films are not taken.

There was not a sufficient number of patients with substantiated pulmonary disease or abnormal pre-operative spirograms to analyze their results with I.P.P.B. separately. Although well established in the treatment of some of these patients in the pre- and post-operative period, the indications should be clear-cut, and the indiscriminate use of I.P.P.B. should be discouraged. Further controlled studies employing a larger number of these patients using I.P.P.B. treatment post-operatively is indicated.

CONCLUSION

1. Intermittent Positive Pressure Breathing, as used in this controlled study by a competent inhalation therapy department, did not prevent post-operative pulmonary

TABLE 8—ABNORMAL PRE-OPERATIVE SPIROGRAM AND ROENTGENOGRAPHIC CHANGE

Abnormal Spirograms	X-Ray Change
Treated Group (6 Cases)	3 minor 0 major
Control Group (9 Cases)	3 minor 2 major

TABLE 9—ANALYSIS OF MAJOR PULMONARY COMPLICATIONS—11 CASES

Factors Aanlyzed	Treated Group (6 cases)	Control Group (5 cases)
Average Age	62 (age 33-80)	45 (age 28-53)
Sex	2 male 4 female	1 male 4 female
Body Build	Endomorph — 3 Mesomorps — 1 Ectomorph — 2	Endomorph — 3 Mesomorph — 0 Ectomorph — 2
Abnormal Pre-Operative Spirogram	0	2
Pre-Operative Pulmonary Disease	1	2 (1 Pulmonary) (1 Coronary)

complications in patients subjected to upper-abdominal surgery. These patients for the most part did not have cardiopulmonary disease.

2. The I.P.P.B. machine as used in this study cannot replace the bedside work of the post-operative surgical team.

3. Although well established in the treatment of some patients with cardio-pulmonary disease in the pre- and post-operative period, the indications should be clear-cut and the indiscriminate use of I.P.P.B. discouraged.

ACKNOWLEDGEMENT: This study was made possible by a grant from Linde Company, Division of Union Carbide Corporation. Acknowledgement is also made to Mrs. Betty Malone for her technical assistance.

CONCLUSIONES

1. El uso de la respiración a presión positiva intermitente como método en estudio controlado por un departamento de terapia de inhalación competente, no previno las complicaciones pulmonares postoperatorias en los enfermos sujetos a cirugía abdominal alta. Estos enfermos en su mayoría no tenían enfermedad cardiopulmonar.

2. La máquina de IPPB como se usó en este estudio, no puede substituir al trabajo a la cabecera del enfermo que desarrolla el grupo de trabajo postoperatorio.

3. Aunque el uso del aparato de IPPB está bien justificado en algunos pacientes con enfermedad cardiopulmonar en el período pre y postoperatorio, sus indicaciones deben ser bien determinadas y su uso indiscriminado debe desalentarse.

RESUMÉ

1. La respiration en pression positive intermittente, utilisée dans cette étude par le service compétent de traitement par inhalations, n'empêcha pas les complications pulmonaires post-opératoires chez les malades soumis à une chirurgie sus-diaphragmatique. Ces malades n'avaient pas d'affection cardiopulmonaire pour la plupart.

2. L'appareil servant à la respiration en pression positive intermittente, utilisé dans cette étude, ne peut pas remplacer le travail au chevet du malade fait par l'équipe chirurgicale post-opératoire.

3. Bien que les indications soient bien établies dans le traitement de quelques malades atteints d'affection cardio-pulmonaire dans la période pré- et post-opératoire, elles devraient être très claires et l'utilisation indiscriminée de la respiration en pression positive intermittente découragée.

SCHLUSSFOLGERUNG

1. Die intermittierende positive Druckatmung, wie sie bei dieser beschränkten Untersuchung durch eine leistungsfähige Abteilung für Inhalationstherapie angewandt wurde, war nicht imstande, postoperative Lungenkomplikationen bei Kranken zu verhindern, die chirurgischen Eingriffen im Oberbauch unterzogen worden waren. Meistenteils hatten diese Patienten keine cardio-pulmonalen Erkrakungen.

2. Die Apparatur zur intermittierenden positiven Druckatmung, wie sie bei dieser Untersuchung benutzt wurde, vermag die Arbeit des Teams zur postoperativen chirurgischen Versorgung am Krankenbett nicht zu ersetzen.

3. Wenngleich klare Indikationen zur Behandlung gewisser Kranken mit Herz-Lungen-Krankheiten durch intermittierende positive Druckatmung während ihrer prä- und postoperativen Periode aufgestellt sind, müssen sie gut abgegrenzt un die wahllose Verwendung dieser Druckatmung verhindert werden.

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Ambulatory Treatment in Tuberculosis Control

The Experience of Puerto Rico

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The experience of Puerto Rico, covering a long period of time devoted to the fight against tuberculosis with limited funds in an adverse environment, brings important lessons to underdeveloped countries with high tuberculosis death rates.

Puerto Rico is one of the most densely populated countries in the world, and at the time when this campaign was started, it was one of

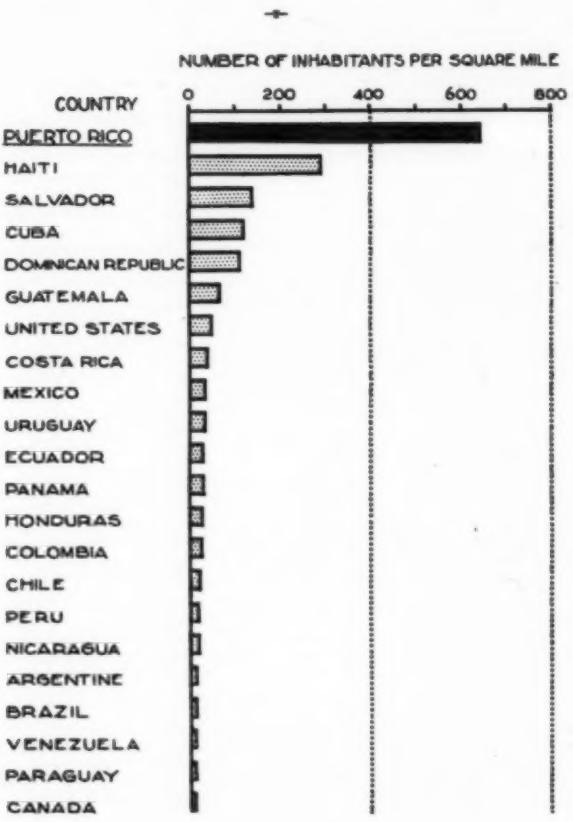

FIGURE 1

*Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, Florida, June 9, 1960.

the poorest. In 1930, the net income per capita was $106 per year, well below the level necessary for mere subsistence. In 1940, it was a little higher, $122 per year. And in 1949, a study made by the Home Economics Department of the University of Puerto Rico[1] revealed that 60 per cent of the families in the island lived on incomes so low that even if they spent all their money for food, they would not be able to purchase the ingredients necessary for a minimum adequate diet. A book about Puerto Rico published in 1947 revealed in its title what the Americans who knew the island well thought about it. The title of the book was *The Stricken Land.*[2]

Housing conditions in the 30's were disastrous, and two recent hurricanes had made them worse. A survey of a slum in San Juan made in 1935 revealed that there was an average of four persons huddled together in each small room. The problem was not only one of many people crowded together in one small dwelling, but of many dwellings crowded into a small tract of land. Such a situation, which was prevalent in every town of the island, was ideal for the spread of tuberculosis. Taking this into consideration, it is not surprising that the tuberculosis death rate

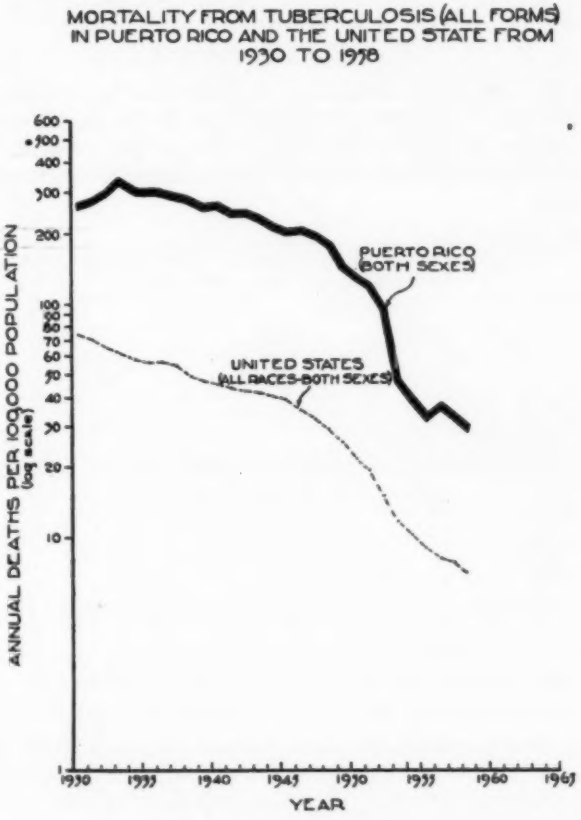

FIGURE 2

reached the almost epidemic figure of 333 deaths per 100,000 population in 1933. What is surprising is that in 1955, just 22 years afterward, this high death rate had been reduced 90 per cent.

We cannot claim that all this great decline in the tuberculosis death rate since 1933 has been due to the campaign against tuberculosis, because there have been great and profound changes in the social and economic conditions of the island during the past 20 years that have played an important part in bringing about the control of all infectious diseases, including tuberculosis;[3] but the fact remains that the standard of living in Puerto Rico is still far below what it is in countries like the United States, and that there exist still in the island the conditions of poor housing, overcrowding and extreme poverty that make for high rates of tuberculosis mortality. It is because of the remarkable decline in the tuberculosis death rate in spite of continued adverse living conditions that the experience of Puerto Rico becomes important to the rest of the world. It offers clear evidence that tuberculosis can be controlled to a large extent by public health methods in the midst of adverse social and economic conditions, and that it is not necessary for underdeveloped countries to wait until the millenium is reached before dealing a death blow to the white plague.

Mortality and Morbidity

During the nine years from 1950 to 1958, the tuberculosis mortality rate came down 77 per cent in Puerto Rico. In the same period of time, the tuberculosis morbidity rate came down 65 per cent. In the United States, the rates were much lower, but the decline through the years was less dramatic.

TABLE 1—PUERTO RICO—TUBERCULOSIS MORTALITY AND MORBIDITY*
Rates per 100,000 pop., 1950 and 1958

Year	Mortality		Morbidity	
	No. of Deaths	Rate	No. of Cases	Rate
1950	2861	130	5866	258
1958	685	29.6	2570	90

*Morbidity in this table refers to newly reported active and probably active cases.

TABLE 2—UNITED STATES—TUBERCULOSIS MORTALITY AND MORBIDITY*
Rates per 100,000 pop., 1952 and 1958

Year	Mortality Rate	Morbidity Rate
1952	15.8	55
1958	7.1	36.4

*Morbidity in this table refers to newly reported active and probably active cases.

In 1950, tuberculosis held the second place among the causes of death in Puerto Rico, and caused 13 per cent of all deaths. In 1958, it had been relegated to eighth place, and it caused only 4 per cent of all deaths.

As in the United States, the most marked decline in tuberculosis morbidity in Puerto Rico has occurred in the productive ages, mainly in the age-group 15 to 24. Although the morbidity has declined at all ages, the decline has been considerably less marked in the age-group below five,

TABLE 3—THE NINE MAIN CAUSES OF DEATH IN PUERTO RICO
Years 1950 and 1958

Year 1950		Year 1958	
Cause	Per Cent of Total Deaths	Cause	Per Cent of Total Deaths
Diarrhea and Enteritis	14	Heart Diseases	16
TUBERCULOSIS	13	Cancer	11
Heart Diseases	11	Diarrhea-Enteritis	9
Pneumonias	8	Pneumonias	7
Cancer	6	Vascular Lesions	6
Certain Diseases of Early Infancy	4	Certain Diseases of Early Infancy	6
Vascular Lesions	3	Accidents	5
Nephritis	3	TUBERCULOSIS	4
Accidents	2	Nephritis	1

and in those above 65. The age specific case rate is relatively higher under five, becomes lower in the age-group 5 to 14 and then rises with age to become highest in persons above 65.

AVERAGE ANNUAL MALE AND FEMALE AGE SPECIFIC MORTALITY FROM TUBERCULOSIS (ALL FORMS) IN PUERTO RICO DURING CERTAIN SPECIFIED TIME INTERVALS

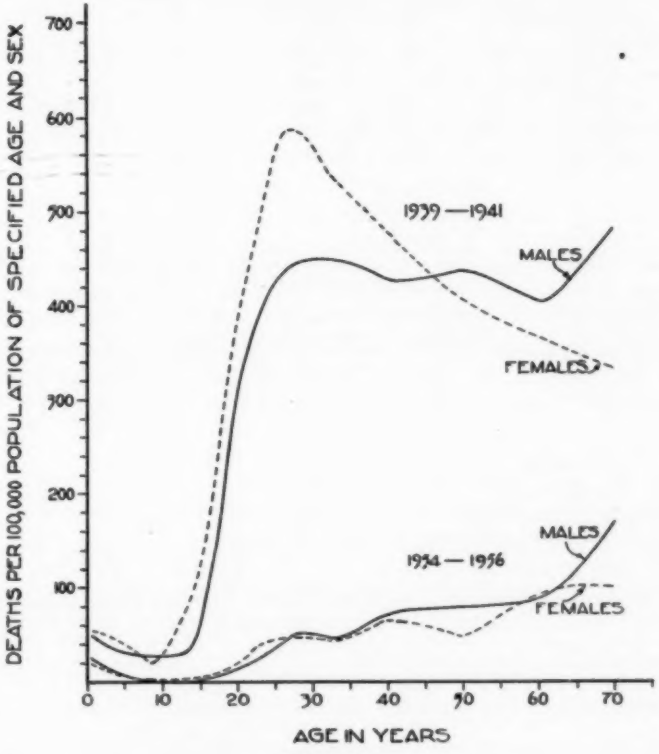

FIGURE 3

The mortality curve also shows the most marked decline in the productive ages, with relatively little improvement through the years in the age-group below five. After the very low rates of the age-group 5 to 14, the curve rises steadily to its peak beyond the age of 65. In the 30's mortality was much higher for females than for males. Now it is becoming higher for men, especially after the age of 40. Differences in mortality between urban and rural populations, and between the white and the colored races, which were very pronounced before 1940, have become less marked as the mortality from the disease declines. In all the groups of population, the higher rates have come down faster.

Tuberculin Sensitivity

In 1935, more than 94 per cent of all the urban dwellers beyond the age of 20 in Puerto Rico reacted to the tuberculin test. More than 65 per cent of children from ages five to nine, and more than 35 per cent of those under five, gave positive tuberculin reactions in the urban communities.[4,5,6]

TABLE 4—TUBERCULIN SENSITIVITY IN URBAN COMMUNITIES OF PUERTO RICO IN 1935

Intradermal Tests with 0.1 mg. and 1 mg. O.T.
Number of Persons Tested, 4,025

Age-Group	No. Tested	Per Cent of Reactors
Under one	109	22
1 - 4	492	38
5 - 9	640	66.6
10 - 14	565	82
15 - 19	486	90.6
20 - 29	706	94.5
30 - 40	430	98.3
Over 40	597	96

TABLE 5—TUBERCULIN SENSITIVITY AMONG URBAN DWELLERS IN PUERTO RICO, 1935

Intradermal Tests with First and Second Dose Strengths of PPD Tuberculin
Number of Persons Tested, 1,767

Age-Group	No. Tested	Per Cent Reactors
0 - 4	128	40.6
5 - 9	348	71.6
10 - 14	608	92.6
15 - 19	314	94.6
20 - 29	147	98
30 - 39	92	98
40 or more	130	96

TABLE 6—TUBERCULIN SENSITIVITY IN PUERTO RICO, 1949-51
Reactions to 1 TU and 10 TU of PPD

Age-Group	Persons Tested	Tuberculin Reactors	Per Cent Reactors
1 - 6	25,103	3,906	15.5
7 - 12	95,114	35,869	37.7
13 - 18	71,610	42,494	59.3
Total	191,827	82,269	43

In contrast with the above, an extensive tuberculin survey done in 1949-51 among more than 190,000 children and adolescents between the ages of one and 18 gave a much lower proportion of reactors,[7] as shown in Table 6.

When we compare this incidence of tuberculin reactors with the results of tuberculin surveys in the continental United States, where only 5 per cent of Navy recruits reacted to tuberculin in 1958-59,[8] we get a better dimension of the problem we still have before us. However, it is quite probable, as Palmer and his associates have pointed out,[7] that a fairly high proportion of the tuberculin reactions obtained in Puerto Rico are due to non-specific tuberculin sensitivity rather than to tuberculous infection. This should be clarified as soon as possible, by carrying out new surveys, using a single dose of 5TU (0.0001 mg.) of PPD-S intradermally, and reading as positive only those reactions that exceed 8 millimeters in diameter, as is done in the Navy. Such a procedure would eliminate most of the non-specific reactions and would give a truer idea of the situation. Studies should be made among large sectors of the population, both urban and rural, to compare the prevalence of tuberculin sensitivity, as revealed by the intradermal test with PPD-S, with the sensitivity to PPD antigens prepared from other acid-fast organisms, such as the Battey mycobacterium.[10,11]

Case Finding in the Tuberculosis Centers

It is interesting to note how the proportion of cases discovered in case finding surveys has been gradually diminishing through the years. At the beginning of the program, this proportion was exceedingly high. In the fiscal year 1935-36, for example, 13,192 persons were examined and nearly one third of them (31 per cent) were found to have pulmonary tuberculosis. A large proportion of these persons, of course, were suspected cases and contacts of known cases of tuberculosis, but even among the general population, the incidence of the disease was very high. These were the years when some of our cities had tuberculosis death rates that exceeded 500 deaths per 100,000 population. In 1938-39, 50,119 persons were examined and 5,648 (11 per cent) were found to have tuberculosis.* Of the positive cases, 2,090 (37 per cent) were found to be suitable for pneumothorax therapy. The rest (63 per cent) were far advanced bilateral or old fibroid cases, or minimal cases that could be treated with bed rest.

In the fiscal year 1939-40, 76,932 persons were examined and 5,908 (7.6 per cent) were found to have tuberculosis. Forty-four per cent of these cases were found to be suitable for pneumothorax treatment.

In recent years, the case finding program has been extended to include photofluorographic examinations of the chest of more than 300,000 persons every year. Cases revealing suspicious shadows by this method are re-examined, using large x-ray films, whenever possible. By these means, the proportion of cases found during the past five or six years has never exceeded six cases per 1,000 x-ray films taken, which is six-tenths of 1 per cent. Even allowing for incomplete diagnoses because of

*About three-fourths of the tuberculosis cases found in these surveys were classified as moderately or far advanced.

failure to follow up all the suspicious cases, or a large proportion of them, it is evident that the number of cases of pulmonary tuberculosis in Puerto Rico does not exceed 1 per cent of the general population. This is indeed a great improvement, when you think of conditions 25 years back.

The Treatment Campaign

The campaign of our Health Department against tuberculosis may be said to have started with the organization of the Bureau of Tuberculosis in 1924, but it was not until ten years later that the intensive treatment campaign was organized.[13]†

There were only about 550 hospital beds available for cases of tuberculosis at this time. Urgent appeals to the Legislature led to the building of ten new hospital units totalling 1,000 beds. Since there was no hope of obtaining more funds for the isolation of the many thousands of contagious cases in the island, it was decided to set up a series of dispensaries, and to treat patients ambulatorily with artificial pneumothorax. This was an ambitious project. There was scarcely any precedent at that time for such sweeping public health measures as the treatment of thousands of cases of tuberculosis with artificial pneumothorax in dispensaries. The only place in North America where such a method was being tried on a fairly large scale was the Municipal Tuberculosis Sanitarium at Chicago. As chief of the Bureau of Tuberculosis of the Insular Health Department, the author had the privilege of visiting that fine institution, and some of the policies and techniques of their work were later incorporated in our system.

Ten tuberculosis centers were organized for the treatment of ambulatory patients with pneumothorax. The first one was opened in May of 1935, and others followed soon after that. Eventually, the number was extended to 20. Each center was well equipped with a fluoroscope and facilities for the taking of x-ray films of the chest, as well as with proper equipment for pneumothorax work. A number of physicians were trained in tuberculosis work at one of the hospitals, and were then placed at the head of the different centers. Each center had visiting nurses, a social worker and a secretary.

It might be interesting to mention here the system that was followed in supervising the work of these dispensaries. Since artificial pneumothorax is a delicate and potentially dangerous procedure, it was felt that systematic supervision of all the cases treated was essential to prevent unnecessary failures and accidents. A panel of supervisors, including the chief of the Bureau of Tuberculosis, the chief radiologist of the Health Department and specialists from the neighboring centers, visited each tuberculosis center regularly to evaluate every case under treatment. The conference began promptly at eight o'clock in the morning and lasted until every case had been reviewed. Each case was reviewed carefully. Inquiries were made concerning bacteriologic examinations of the sputum before and after treatment. All x-ray films were examined and

†The greater part of the credit for this remarkable public health campaign belongs to the late Dr. Eduardo Garrido Morales, Commissioner of Health of Puerto Rico from 1933 to 1943, one of the most devoted and efficient public servants that our island ever had.

records were reviewed for accuracy and completeness. All the physicians present were encouraged to criticize and make suggestions. The disposition of each case was then decided. After the examination of all the cases had been completed, the work of the center was given a rating according to a scale which granted a number of points for each case treated. A well-managed case merited ten points. If the treatment was right, but the reports of the sputum examinations were not up to date, or the x-ray films were of poor quality, the case might rate five or seven points. A case that had to be discontinued by the panel because of poor management would get 0. The total score would give an idea of the quality of the work done in each center. Cases were also classified as "satisfactory," "fairly satisfactory" and "unsatisfactory." The center getting the best score at the end of the year would be given a silver cup with an inscription, and this would be the occasion for a celebration in which physicians from other centers would participate.

This plan of supervision and encouragement gave the physicians a certain pride in their work, and made it possible for each one to learn something from the experience of others. It led to constant improvement in methods and techniques, and prevented many serious errors.

Several studies were made to find out the effectiveness of the treatments given.[12] The first one of these was made in 1936. It was based on an analysis of the results obtained in 915 patients who had been selected for pneumothorax treatment the first year of the program. It was found that 40 per cent of these patients were doing well and had become sputum negative after a few months to a year of treatment. In a total of 22,300 pneumothorax insufflations, there had been 20 accidents, mainly "pleural shock" and air embolism. None of these had been fatal.

In 1937, 2,982 patients were treated with pneumothorax in the tuberculosis centers, including those that had been brought over from 1935 and 1936. Sputum conversion was attained in 41 per cent.* There were 53 accidents, three of them fatal. The fatalities and most of the accidents were probably due to air embolism, although many of them were attributed to "pleural shock."

In 1938, a study was made of 3,824 tuberculous patients who had been selected for pneumothorax treatment in the centers during the previous three years. In 364 of them, pulmonary collapse could not be induced because of pleural symphisis. Pneumothorax was administered to 3,460 for various lengths of time. Forty-six per cent were given the treatment for six months to one year, and 27 per cent for more than one year. Successful collapse with closure of cavities** and sputum conversion was attained in 33 per cent of all the cases treated. Nine per cent had pleurisy with effusion as a complication of pneumothorax, and about one-fifth of the pleurisies were purulent.

Routine revision of all the cases treated in the tuberculosis centers over the course of seven years revealed that at least 50 per cent of those

*Sputum examinations at this time did not include cultures, except in special cases. Concentrated sputum specimens were examined for tubercle bacilli before pneumothorax treatment and every month after that, until expectoration stopped.

**Cavity closure was determined on the basis of flat x-ray films of the chest. An x-ray film of the chest was taken routinely every month on every patient under treatment. Patients were fluoroscoped before and after each pneumothorax insufflation.

who received pneumothorax for more than six months derived lasting benefit, including disappearance of symptoms, persistently negative sputum smears and inactivation of the lesion as demonstrated by x-ray films. Among those treated for more than one year, this proportion was considerably higher. It must be kept in mind that over three-fourths of all patients treated in the dispensaries were in the advanced stages of the disease.

Drug Therapy

Since the treatment of ambulatory cases began in 1934, the methods and techniques of treating tuberculosis have changed repeatedly, and every new method has been incorporated into the campaign. In 1949, treatments with drugs were started in the dispensaries. Streptomycin and PAS were given free of charge to all active cases.

When isoniazid became available in 1952, large purchases of the drug were made by the Health Department and it was given free of charge to all active cases, substituting for PAS. The combination of drugs used since that time has been isoniazid (average daily dose, 300 mg.) and streptomycin, one gram intramuscularly twice a week, with PAS in some cases. Pneumothorax, and later pneumoperitoneum, were continued on a smaller scale.[14]†

Any patient afflicted with tuberculosis has the right to go to a dispensary to get free treatment with drugs without any questions being asked concerning his economic status. Treatments are given in courses of three months. At the end of each course, the case is reviewed by the physician and a new course of treatment is prescribed, if indicated. The aim is to give the treatment for two years or more. Those requiring surgery are referred to a tuberculosis hospital equipped for such work.

It is estimated that 22,000 cases of tuberculosis (active and inactive) are registered in our tuberculosis centers. The great majority of them have received free drug treatments at one time or another. At the end of the year 1958, nearly 7,800 ambulatory patients were receiving drug therapy in the centers.[15] About 2,600 additional patients were being treated in public and private tuberculosis hospitals.

Estimates as to the proportion of ambulatory patients improved or cured with these mass drug treatments vary from 39 per cent to more than 60 per cent. The results differ with each tuberculosis center and depend largely on the administrative efficiency of the dispensary, and on the quality and number of its technical personnel, especially the doctors and nurses. The appraisal of results is made difficult by the lack of adequate bacteriologic studies of the sputum in the patients treated.

Pamplona, *et al.*[16] studied the records and x-ray films of 172 patients from seven tuberculosis centers who had begun drug therapy during the three-month period from July 1 to October 1, 1955. Since the study was made in February of 1957, this interval provided for 16 to 20 months of supervision. They found that 39 per cent of the patients treated showed improvement.[11]

†During the last few years collapse therapy has been practically abandoned in the tuberculosis centers.

Heimann[17] made a study of 1,000 x-ray films of the chest from cases treated in the dispensaries, and found evidence of radiologic improvement in 50 per cent.

Another study of 100 consecutive cases under drug therapy in three dispensaries showed evidence of radiologic improvement in 67.[18]

These and other attempts at appraisal are incomplete and by no means definitive. Complete studies on the results of drug therapy in substantial numbers of dispensary patients in Puerto Rico are yet to be made.

In New York City, Robins, *et al.*[19,20] studied 1,146 non-hospitalized tuberculous patients who received at least four months of drug therapy in the chest clinics of the New York City Department of Health. After one year of observation, 56 per cent of the patients with sputum initially positive gave negative sputum cultures. Roentgenographic improvement was noted in 47 per cent, and 35 per cent were considered "arrested." After two years of observation on 351 of these patients, the proportion of arrested cases was 48 per cent.

Research on BCG Vaccination

Mass vaccination with BCG has never been used as a public health procedure in Puerto Rico. However, extensive research work on BCG was begun in the island in the fall of 1949 under the auspices of the United States Public Health Service, as part of a larger investigation that included parts of the states of Georgia and Alabama. The study was carried out under the direction of Drs. Carroll E. Palmer; Lawrence W. Shaw and George W. Comstock, with the cooperation of the Health Department of Puerto Rico. The study included 165,000 children and adolescents, and over 50,000 of them were vaccinated with BCG.[7] The details of this remarkable study have been published elsewhere.[7,8] Suffice it to say that after nine years of follow-up of the vaccinated, as well as the unvaccinated subjects, the investigators have concluded that BCG vaccination is not the answer to the problem of tuberculosis in Puerto Rico or in the United States. They found that the risk of developing tuberculosis is three times greater for tuberculin reactors than for non-reactors. Three out of every four cases of tuberculosis that occurred during the follow-up period were found among the subjects that had reacted to tuberculin at the beginning of the study. Only 6 per cent of the cases could have been prevented by BCG vaccination had all the non-reactors been vaccinated. The conclusions of the investigators are summarized in the following paragraph from one of their reports:[7]

"Because BCG vaccination cannot help those who are already infected, nor those who will not become infected, and may be helpful only to a portion of the decreasing few that will become infected in the future, it is apparent that vaccination cannot be very useful in controlling tuberculosis in this country. Moreover, with the rapid decline in tuberculous infection, the tuberculin test is becoming increasingly more valuable for epidemiologic, case-finding and diagnostic purposes. These uses of the tuberculin test are destroyed by vaccination, which makes it virtually impossible to identify the naturally infected persons. And, as those who are already infected are now the group at greatest risk, it is upon

them that the tuberculosis control activities should be focused if the disease is to be eradicated. The position is taken that in most situations in this country today the advantages of vaccination are outweighed by the disadvantages."

Plans for the Future

Plans are now being made by the Health Department[15] for the reorganization of some aspects of its campaign against tuberculosis. The tuberculin test is to be used extensively as a screening procedure in all children under 12, to be followed by x-ray film studies of all reactors. Some of this has been done always, but the new plan calls for an all-out campaign in this respect. Tuberculin reactors under the age of two years will be given isoniazid for one year. Preventive treatments with isoniazid will be given also for one year to all contacts of tuberculous patients, whenever overcrowding and poor housing conditions facilitate contagion.

The management of drug therapy in dispensaries will be reorganized to provide for more effective follow-up of patients, more complete bacteriological studies, more home visiting, better supervision and systematic evaluation of all cases under treatment. PAS will be used routinely in all patients who can tolerate the drug, in addition to isoniazid and/or streptomycin.

Better coordination between the dispensaries and the hospitals in the management of patients under treatment will be assured by giving the Chief of the Bureau of Tuberculosis the authority needed to control discharges and admissions in all the tuberculosis hospitals.

Discussion

Even with the best possible organization, the dispensary is not the ideal place to treat active contagious cases of pulmonary tuberculosis. The hospital is much better, and wherever conditions permit, treatments should be started in hospitals rather than in dispensaries. Where the number of active cases is so large and the number of hospital beds so inadequate that patients have to choose between getting treated in dispensaries or running the chance of becoming incurable before securing admission to hospitals, there is no question as to which course of action is preferable. Dispensaries then become absolutely necessary as places where the great majority of patients must be treated as soon as their lesions appear. Prompt treatment, even when not too good, is better than the best treatment given too late.

Our great handicap in Puerto Rico, since the beginning, has been the lack of sufficient hospital beds. There is always a certain proportion of cases of pulmonary tuberculosis that require surgery, and unless the facilities for surgery are available at the proper time, these cases may become incurable. Proper coordination between the dispensary and the hospital is indispensable for the success of any program of dispensary treatments.

In our experience, drug therapy has proved much more effective than collapse therapy as a public health measure for the control of the spread of infection in pulmonary tuberculosis. Drug treatment can be given to everyone, whereas collapse therapy can be given only in selected cases. The complications of collapse therapy are more serious and more frequent than those of drug therapy. Also, collapse therapy is more expensive and more difficult to give. The combination of drugs now being used in our dispensaries (daily isoniazid with SM twice a week) is ineffective in many advanced cases. Such cases respond much better to daily streptomycin with isoniazid. Since daily streptomycin is difficult to administer in dispensaries, it would be better to treat all advanced cases with INH and PAS. However, many patients cannot tolerate PAS. Such treatments require close medical supervision.

The great epidemiologist, Wade Hampton Frost,[21] once made a remark that has been often quoted. "For the eventual eradication of tuberculosis," said Frost, "it is not necessary that transmission be immediately and completely prevented. It is necessary only that the rate of transmission be held permanently below the level at which a given number of infection-spreading (*i.e.*, open) cases succeed in establishing an

equivalent number to carry on the succession. If, in successive periods of time, the number of infectious hosts is continuously reduced, the end result of this diminishing ratio, if continued long enough, must be extermination of the tubercle bacillus."

This dictum of Frost may explain our rapidly declining mortality and morbidity from tuberculosis in spite of the fact that our ambulatory treatments have failed to cure perhaps one-half of the cases treated. The explanation is that the number of infectious hosts has been reduced continuously in the island for a period of 25 years through the persistent effort to treat every case as soon as it is diagnosed. Even though only a portion of the contagious cases could be controlled, the persistent campaign year after year has resulted in a diminishing ratio of transmission and the effective control of the disease. A more efficient system would have resulted in greater achievements, but with our limitations, the results are impressive.

Investigations such as those made by Palmer and his associates[7] on BCG vaccination seem to lead to the conclusion that the right approach to the problem of tuberculosis is the one that has been pointed out repeatedly by Dr. J. Arthur Myers of Minnesota.[22-24] During nearly 40 years, Dr. Myers has been carrying on epidemiologic and clinical investigations intended to point the way to the solution of the public health problems confronting the tuberculosis worker. He began by demonstrating the importance of the tuberculin test as a diagnostic and epidemiologic tool. He pointed out that the proper time to treat tuberculosis is soon after infection sets in, that is, soon after the tuberculin test becomes positive, and before desstructive reinfection lesions have developed. He warned against mass vaccination with BCG at a time when the whole world seemed to think that this was the method of choice for eradicating tuberculosis. He warned that BCG vaccination would destroy the usefulness of the tuberculin test and that it would be ineffective for the control of tuberculosis because it would leave without protection those that needed it most—the tuberculin reactors, who were in the greatest danger of acquiring fatal disease. He defended the classical measures of early diagnosis, isolation, early treatment and education as the only reliable means for eradicating the tubercle bacillus. Others have held these same views, but no one has defended them with the same persistence and authority.

From now on, the treatment of tuberculosis will start with the tuberculin reactor. The campaign that is now being planned in Puerto Rico for the treatment of recent reactors and contacts of open cases with isoniazid is a good indication of the new attitudes. The prompt treatment of every case of tuberculosis at the earliest possible time will be the main control procedure. Anything that may interfere with the discovery of the early case will be considered a backward step in tuberculosis control. BCG vaccination, with its tendency to mask the signs of natural infection, will be discarded in most countries in favor of tuberculin surveys and early treatment of reactors with antimicrobial drugs.

Back in 1934, those of us who were fighting tuberculosis in Puerto Rico dreamed that some day in the not-too-distant future we might be able to treat every case of tuberculosis in its incipiency. We were mistaken. After all these years, our case-finding surveys continue to reveal too many advanced cases that have gone undiscovered for too long. It is evident that the x-ray machine, the laboratory and the clinical examination, so helpful in many other ways, have failed to show us the way to the discovery of the incipient case; not the so-called minimal case, which may be the end rather than the beginning of the story, but the really incipient case. Only one method remains for us to trust: the tuberculin test. In spite of the prevalence of non-specific tuberculin sensitivity in some areas, the tuberculin test gains in stature with the years. It may still lead us to the realization of that old dream: the discovery and treatment of every case of tuberculosis before it is too late.

SUMMARY

Tuberculosis mortality declined in Puerto Rico from a rate of 333 deaths per 100,000 population in 1933, to 29.5 in 1959. This remarkable improvement was due largely to an intensive campaign which consisted of case-finding, education and early treatment of new cases. Since facilities for the hospitalization of open cases were very inadequate, it was decided in 1934 to treat most cases in dispensaries, using artificial pneumothorax as the main therapeutic procedure.

Pneumothorax (used since 1935) was effective in closing cavities and converting the sputum in 33 to 40 per cent of all the ambulatory patients selected for this treatment. Among those who took the treatment for six months or longer, the proportion of arrested cases was higher than 50 per cent. Since thousands of cases were treated, the total effect on the prevention of contagion was important.

Antimicrobial therapy has been used extensively since 1949. Streptomycin and PAS were the first drugs used. Practically every case of tuberculosis attending the public health dispensaries is now given antituberculous drugs (streptomycin and isoniazid) as soon as the diagnosis is made. In most cases the treatment has been continued for periods of six months or longer. Evaluation of the results obtained with these mass treatments have not been done on a large scale, but the limited studies made seem to indicate that about one half of the cases treated receive lasting benefit. Since the number of cases treated with drugs averages over 8,000 per year, the total effect of

the program on the prevention of contagion has been of great importance. Reorganization of administrative procedures now being planned will undoubtedly improve results.

Plans of the Health Department for next year include tuberculin testing of all children under two, and treatment of reactors with isoniazid for one year; also tuberculin testing and treatment with isoniazid for one year of all contacts under 12 who live in conditions that facilitate contagion.

BCG vaccination research done in Puerto Rico and other parts of the Union under the auspices of the United States Public Health Service has shown that mass vaccination with BCG is ineffective and undesirable as a procedure for tuberculosis control. Well known public health measures that have stood the test of time, such as intensive case finding, prompt treatment of new cases and education, continue to be the pillars of the tuberculosis campaign. In the years to come, the treatment campaign will probably begin with the tuberculin reactor. It seems quite probable that the prompt treatment of tuberculin reactors with antimicrobial drugs will replace BCG vaccination in many countries.

RESUMEN

La mortalidad por tuberculosis declinó en Puerto Rico desde 333 muertes por 100,000 habitantes en 1933 hasta 29.5 en 1959. La notable mejoría se debe en gran parte a la campaña intensa de búsqueda de casos, educación y tratamiento temprano de los casos nuevos. Puesto que las facilidades para la hospitalización de los casos abiertos eran muy inadecuadas se decidió en 1934 tratar la mayoria de los casos en el dispensario usando el neumotorax artificial como medida terapeutica principal.

El neumotorax, (usado desde 1935) fue efectivo para clausurar cavernas y convertir el esputo en 33 o 40 por ciento de todos los casos ambulatorios escogidos para ese tratamiento.

Entre los que siguieron el tratamiento por seis o mas meses la proporción de casos en que se obtuvo la detención de la enfermedad fue mayor de 50 por ciento. Ya que se trataron millares de enfermos así, el efecto global para la prevención del contagio fué importante.

La terapéutica antimicrobiana se usó ampliamente desde 1949. La estreptomicina y el PAS fueron las primeras drogas usadas. Practicamente todos los casos de tuberculosis que asisten a los dispensarios de Salud Pública, reciben ahora drogas antituberculosas (estroptomicina e insoniacida) tan pronto como se have el diagnóstico.

En la mayoría de los casos el tratamiento se ha continuado por períodos de seis o mas meses. La valuación de los resultados obtenidos con estos tratamientos en masa no se ha hecho en gran escala pero los estudios limitados parecen indicar que aproximadamente la mitad de los casos recibieron beneficio duradero. Puesto que el número de casos tratados con drogas es mayor de 8,000 por año, el efecto total del programa en la prevención del contagio ha sido de gran importancia. La reorganización de los procedimientos administrativos, que ahora se proyecta, dará indudablemente mejores resultados.

Los planes de la Salubridad Pública para el año entrante incluyen la prueba tuberculínica en todas los niños menores de dos años y el tratamiento de los reactores con isoniacida por un año. También la prueba tuberculínica y el tratamiento por un año de todos los contactos menores de 12 años que vivan en condiciones que faciliten el contagio.

Estudios sobre la vacunación con BCG en Puerto Rico y en otras partes de la Unión bajo los auspicios de la Salubridad Pública de los Estados Unidos han mostrado que la vacunación en masa con BCG es inefectiva e indiseable para el control de la tuberculosis.

Los procedimientos bien conocidos de salubridad que han resistido la prueba del tiempo tales como la busqueda pertinaz de los casos, el tratamiento inmediato y la educación, continúan siendo los pilares de la campaña de tratamiento que en el futuro empezará probablemente con el reactor tuberculínico. Parece muy probable que el tratamiento inmediato de los reactores tuberculínicos con drogas antimicrobianas substituirá a la vacunación con BCG en muchos paises.

RESUMÉ

La mortalité tuberculeuse est tombée à Puerto-Rico d'un taux de 333 morts pour 100,000 h. en 1933 à 29.5 en 1959. Cette amélioration remarquable est largement imputable à une campagne intensive qui a comporté dépistage, éducation sanitaire et traitement précoce des nouveaux cas. Comme les possibilités d'hospitalisation pour les cas contagieux se montraient très insuffisantes, il fut décidé en 1934 de traiter la plupart des cas dans les dispensaires, en utilisant le pneumothorax artificiel comme traitement principal.

Le pneumothorax (utilisé depuis 1935) fut efficace pour fermer les cavités et négativer l'expectoration dans 33 à 40% de l'ensemble des malades ambulatoires choisis pour ce traitement. Parmi ceux qui subirent ce traitement pour six mois ou plus, la proportion des cas jugulée fut de plus de 50%. Comme des milliers de cas furent traités, l'effet total sur la prévention de la contagion fut important.

La thérapeutique antimicrobienne fut utilisée extensivement depuis 1949. La streptomycine et le PAS furent les premières drogues utilisées. Pratiquement chaque cas

de tuberculose relevable des dispensaires de la santé publique reçoit maintenant des produits antituberculeux (streptomycine et isoniazide) dès que le diagnostic est fait. Dans la plupart des cas, le traitement a été poursuivi pendant une période de six mois et plus. L'évaluation des résultats obtenus avec ces traitements de masse n'a pas été faite sur une large échelle, mais les études limitées semblent indiquer qu'environ une moitié des cas traités en reçoivent un bénéfice durable. Comme le nombre de cas traités avec les produits atteint plus de 8,000 par an, l'effet total du programme sur la prévention de la contagion a été de grande importance. La réorganisation des moyens administratifs étant actuellement envisagée les résultats se trouveront sans doute améliorés dans l'avenir.

Le programme du Ministère de la Santé pour l'année prochaine comprend la pratique des tests tuberculiniques pour tous les enfants de moins de deux ans, et le traitement des enfants à réaction positive par l'isoniazide pendant un an; ainsi que la réaction tuberculinique et le traitement par l'isoniazide pendant un an de tous les contaminés de moins de douze ans, qui vivent dans des conditions que facilitent la contagion.

L'étude de la vaccination par le BCG faite à Porto-Rico et dans d'autres régions de l'Union sous les auspices du Ministère de la Santé Publique des Etats-Unis a montré que la vaccination de masse par le BCG est inefficace et indésirable comme moyen de contrôle pour la tuberculose. Dese mesures bien connues concernant la santé publique quie ont passé l'épreuve du temps, telles que dépistage intensif, traitement précoce des nouveaux cas, et éducation du public, continuent à être les piliers de la campagne contre la tuberculose. Dans les années à venir, la campagne de traitement commencera probablement par les porteurs de réactions positives à la tuberculine. Il semble assez probable que le traitement précoce des porteurs positifs avec les produits antimicrobiens remplacera la vaccination par le BCG dans beaucoup de pays.

ZUSAMMENFASSUNG

Die Tuberkulosesterblichkeit fiel in Puerto Rico von einer Zahl von 333 Todesfällen auf 100,000 Einwohner im Jahre 1933 auf 29.5 im Jahre 1955. Diese bemerkenswerte Besserung war zum großen Teil die Folge eines intensiven Feldzuges, bestehend auf der Suche nach Erkrankten, in einer Erziehung und in der Frühbehandlung von neuen Fällen. Da die Möglichkeiten für die stationäre Behandlung offener Fälle sehr unzulänglich waren, beschloß man in Jahre 1934, die meisten Fälle in ambulante Behandlung zu nehmen unter Einsatz des künstlichen Pneumothorax als der hauptsächlichen therapeutischen Methode.

Der (seit 1935) in Gebrauch befindliche Pneumothorax ist von guter Wirksamkeit bezüglich Kavernenverschluß und Bazillenfreiheit bei 33 - 40% aller für diese Behandlung ausgewählten ambulanten Kranken gewesen. Bei denjenigen, bei denen die Behandlung 6 oder mehr Monate durchgeführt werden konnte, war das Verhältnis der zum Stillstand gebrachten Fälle größer als 50%. Nachdem 1000 von Kranken behandelt worden sind, war die Gesamtwirkung der Verhinderung der Ansteckung bedeutend.

Die antimikrobielle Therapie wurde ab 1949 in ausgedehntem Maße angewandt. Streptomycin und PAS waren die ersten der eingesetzten Mittel. Praktisch jeder Fall von Tuberkulose, der sich in die Sprechstunde des Gesundheitsamtes begibt, erhält jetzt antituberkulöse Mittel (Streptomycin und INH), sobald die Diagnose gestellt ist. In den meisten Fällen wurde die Behandlung über Zeiträume von 6 und mehr Monaten fortgesetzt. Eine Auswertung der Resultate, wie sie mit dieser Massenbehandlung erzielt wurden, ist auf breiter Basis noch nicht gemacht worden, jedoch scheinen die begrenzten Untersuchungen zu ergeben, wie sie inzwischen angestellt wurden, daß ungefähr die Hälfte der behandelten Fälle wenigstens eine anhaltende Besserung erfuhren. Da die Zahl der mittels Medikamenten behandelten Fälle bei über 8,000 pro Jahr liegt, so war doch die Gesamtwirkung des Planes zur Verhütung der Ansteckung von großer Bedeutung. Eine Reorganisation der Verwaltungsmaßnahmen, die jetzt vorgesehen ist, wird ohne Zweifel die Ergebnisse noch verbessern.

Die Pläne der Gesundheitsabteilung für das nächste Jahr umfassen Tuberkulinproben bei allen Kleinkindern unter 2 Jahren und Behandlung der positiv Reagierenden mit INH während eines ganzen Jahres; ferner Tuberkulinprüfung und Behandlung mit INH für ein Jahr bei allen Umgebungsfällen unter 12 Jahren, die unter Bedingungen leben, die eine Ansteckung begünstigen.

Forschungen über BCG-Impfungen, wie sie in Puerto Rico und anderen Teilen des Landes unter der Führung des Gesundheitsdienstes der USA erfolgten, haben gezeigt, daß eine Massenimpfung mit BCG unwirksam und nicht wünschenswert ist als Verfahren zur Tuberkulosebekämpfung. Wohl bewährte Methoden des Staatlichen Gesundheitsdienstes, die ihre Bewährungsprobe bestanden haben, wie intensive Suche nach unbekannten Tuberkulosefällen, prompte Behandlung der neuen Fälle und ihre Erziehung, bleiben auch weiterhin die Grundpfeiler des Feldzuges gegen die Tuberkulose. In den vor uns liegenden Jahren wird die Behandlung wahrscheinlich bereits bei dem auf Tuberkulin positiv reagierenden Menschen beginnen. Vieles spricht dafür daß die prompte Behandlung von Tuberkulinreaktoren mit antimikrobiellen Heilmitteln in vielen Ländern die BCG-Impfung ersetzen wird.

Complete reference list will appear in reprints.

Trypsin Therapy in Pulmonary Diseases, 1955-1960

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The role of trypsin as a therapeutic modality for the treatment of inflammation and edema, to liquefy purulent debris and inspissated thick, viscid mucus, has been established.[1-15]

Clinical observations described[4] to document the efficacy of buccally administered trypsin tablets, given in conjunction with intramuscular trypsin, for the rapid control of the signs and symptoms of respiratory infections.

Liquefication of sputum and rapid dimunition of cough were observed[3] in patients with acute and chronic bronchitis and bronchial asthma following the use of intramuscular trypsin.

It has been reported[13] that treatment with intramuscular trypsin, given simultaneously with antibiotics, effected a clinical cure within a period varying from three to six weeks in cases of tuberculous lymphadenitis and bone tuberculosis (sternum and first rib). The author concluded that trypsin, given simultaneously with antituberculosis drugs and antibiotics, appears to be the treatment of choice in tuberculosis lymphadenitis and secondary sinuses, or bone tuberculosis.

After two months of combined treatment with trypsin and antituberculosis drugs and antibiotics, there was a complete resolution of the pulmonary lesion in a patient with miliary tuberculosis and tuberculous meningitis. This result prompted the suggestion[14] that trypsin in sesame oil be considered as an adjunct to antituberculosis drugs and antibiotics in the management of miliary and meningeal tuberculosis.

Our interest in the proteolytic enzymes was initiated in 1955. With passage of time, new pharmaceutical forms of crystalline trypsin were developed in an endeavor to promote patient cooperation. Our studies started with crystalline trypsin in sesame oil (Parenzyme). In 1957, we used buccal tablets of crystalline trypsin (Parenzyme B); in 1958-59, trypsin in aqueous solution (Parenzyme A) and finally in 1959 an enteric coated tablet of trypsin for oral administration (Orenzyme).

We will present our experiences with the various available forms of trypsin along with our results in four groups of patients.

Materials and Methods

The overall study was started in 187 and actually completed in 170 patients. Of the 170, 98 were white and 72 colored; 96 were men and 74 women, whose ages ranged from 18 to 69 years. The disease states treated are listed in Table 1.

TABLE 1—DISEASES TREATED WITH CRYSTALLINE TRYPSIN

Chronic Bronchitis — Bronchial Asthma	59
Bronchiectasis	27
Pulmonary Emphysema	13
Unresolved Pneumonia — Atelectasis	14
Pulmonary Tuberculosis	48
Lung Abscess	9
Total Patients	170

The 170 patients represent the total of the four study groups to be described. A complete history was obtained from each patient—after which a careful physical examination was made.

All had complete blood counts, urinalysis, blood sugar determination, BUN, sedimentation rates and chest x-ray films before enzyme treatment and at least monthly during treatment, and a complete follow-up at conclusion of treatment. Of the 170 patients, 60 had bronchoscopic examinations or bronchograms.

Clinically, evaluation was based on the following criteria:

1. Cough: increased, decreased, or no change.
2. Expectoration: quantity and type.
3. Dyspnea: improved, unchanged, or worse.
4. Exercise tolerance (especially walking): increased, no change, or decreased.
5. Wheezing: increased, unchanged, or decreased.
6. General status: including fever, appetite, emotional status.

Group I: Crystalline trypsin in sesame oil (Parenzyme):

The preparation represented 5 mg. crystalline trypsin per ml.

Fifty-three patients were started on 5 mg. intramuscularly, to be continued on a daily schedule for at least 12 days. After the first several injections, 15 rejected further treatment. Thirty-eight completed the 12 days of trypsin treatment. Since all of these patients had pulmonary tuberculosis, they received concomittant antituberculosis chemotherapy.

Group II: Buccal trypsin tablets (Parenzyme B):

Each tablet contained 5 mg. of crystalline trypsin. Thirty patients with asthma, bronchiectasis or atelectasis were treated with these tablets, one tablet q. 12 hours daily for 14 days. The patients were instructed to place a tablet in the buccal pouch and hold it at this site until completely disintegrated, and not swallow the accumulated saliva for several minutes after the tablet was disintegrated. This interval was required to permit the absorption of the trypsin.

Group III: Crystalline trypsin in a gelatin medium (Parenzyme A):

This material was supplied in a two vial package—one vial containing lyophilized crystalline trypsin, 25 mg.; the second vial, the diluent, made up of 50 per cent denatured gelatin and preservatives methylparaben 0.09 per cent and propylparaben 0.01 per cent. Five ml. of the diluent were withdrawn, with sterile technique, and transferred to the lyophilized trypsin. A clear solution resulted after lightly shaking the vial. Each ml. now contained 5 mg. of crystalline trypsin which had a stability life of three months under refrigeration.

A course of treatment consisting of 5 mg. of trypsin intramuscularly daily for seven days, then 5 mg. every other day for 14 to 21 days was established for all 50 patients in this group. Two developed severe itching and localized rash around the injection site, and treatment was stopped. Patients with chronic disease were allowed a "rest period" of two weeks, then given a second course of treatment. Thirty-two received two to five such courses of trypsin (aqueous) treatment. These patients continued to receive supportive therapy, specific antibiotics, aerosol and/or intermittent positive pressure breathing.

Group IV: Enteric coated tablets of trypsin (Orenzyme):

The tablets consisted of trypsin (68 per cent), chymotrypsin (30 per cent) and ribonuclease (2 per cent), equivalent to proteolytic activity of 20 mg. of crystalline trypsin. They are enteric coated to permit passage through the stomach and disintegration in the upper intestinal tract.

The convenient mode of therapy was used in 54 patients with pulmonary diseases diagnosed as chronic bronchitis, bronchial asthma, bronchiectasis, emphysema, lung abscess and pulmonary tuberculosis. Sixteen were given two or three injections of tryspin (aqueous) intramuscularly, then continued on the enteric coated trypsin to complete the treatment. Thirty-eight were started and continued on the enteric coated trypsin until treatment was completed.

The initial dosage of the tablets was two each four hours for four doses daily for a period of two weeks, then one tablet each four hours for four doses daily for four to six weeks, or until the response was satisfactory.

Clinical Results and Comments

The number of patients started on a therapeutic program, the number rejecting continued treatment and the number in which treatment was completed are shown in Table 2.

TABLE 2

Group	Diagnosis	Treatment	Started Treatment	Refused Treatment	Completed Treatment
I	Pulmonary tuberculosis	Crystalline trypsin in sesame oil—intramuscular, concomittant anti-tuberculosis chemotherapy	53	15	38
II	Bronchiectasis—asthma Atelectasis	Buccal trypsin—5 mg. two tabs daily	30	0	30
III	Chronic bronchitis— Bronchial asthma— Unresolved pneumonia with atelectasis—lung abscess Pulmonary emphysema	Trypsin (aqueous) 5 mg. daily intramuscularly for 7-14 days	50	2	48
IV	Bronchial asthma— Chronic bronchitis— Bronchiectasis— Pulmonary emphysema	Enteric coated trypsin oral 2 tabs. q. 4 hrs. for 4 doses daily 1 tab. q. 4 hrs. for 4 doses daily	54	0	54
		TOTALS	187	17	170

Group I: In the 38 patients continued on trypsin in sesame oil, the sputum became thinner and expectoration was increased the first week of treatment, followed with a decrease in secretions. Wheezing diminished and shortness of breath improved in many of them. There was no apparent effect on the tuberculous process different from that observed in patients without trypsin therapy. Serial x-ray films showed no changes in old chronic cases, whether or not treated with the trypsin preparation. Moderately-advanced tuberculous patients had similar improvements in treated and untreated cases, apparently the results of chemotherapy and hospital care.

Comment: One of our fears, early in the study, was a possible breakdown of fibrous tissue with resultant pulmonary hemorrhage. Although all of these patients had pulmonary cavitations, there was no case of hemoptysis.

In spite of the symptomatic improvements and thinner secretions, it was felt that the local pain and malaise with fever contraindicated its use in this type of patient.

Group II: Thirty patients were started on buccal trypsin tablets—one tablet each 12 hours daily and continued on this schedule for two weeks. Seventeen had irritation of the mouth, five developed superficial ulcerations of the inside of their mouths, and eight had no reactions. The sputum became less tenacious and expectoration was easier—the beneficial effects were, at best, minimal.

Comment: It is our impression that the buccal trypsin afforded only minimal improvement in pulmonary diseases, with too many occurrences of local side effects.

Group III: Fifty patients were originally started on Parenzyme aqueous. Two developed severe itching and local rash around the injection site, and treatment was stopped. Of the 48 who were continued on this trypsin treatment:

1. Eleven showed marked improvement in such conditions as unresolved pneumonia with atelectasis, lung abscess, chronic bronchitis with bronchial asthma and pulmonary emphysema.
2. Twenty with similar pathology showed moderate improvement.
3. Twelve showed minimal improvement.
4. Four showed no improvement.
5. One, with one course of treatment, believed his condition was worse.

Since there was no change in the laboratory findings, improvement was evaluated by x-ray film and clinical changes. There was definite evidence of clearing on x-ray films in 13, especially in comparatively recent atelectasis and obstructed lung abscesses. It must be realized that x-ray film changes usually are not as rapid as clinical findings.

There was no incompatibility with any of the number of antibiotics given with the trypsin. Four of the patients had cirrhosis of the liver, one had chronic pyelitis with calculus (staghorn) and three had pulmonary tuberculosis. None of these diseases was aggravated by trypsin treatment.

Comment: Pain and induration at the site of injection was considerably less than that observed in patients treated with trypsin in sesame oil.

Group IV: Long-term evaluation of oral trypsin has not been made since we had not used this preparation over a long enough period of time. Results in 44 of 54 patients, treated with oral trypsin, were most impressive. This form of trypsin served not only as effective maintenance therapy after parenteral trypsin, but seemed to be as effective as trypsin (aqueous) in starting treatment.

Comment: Enteric coated trypsin tablets for oral administration are convenient to use and are apparently as effective clinically in the management of certain pulmonary diseases as the parenteral trypsin aqueous preparation. This oral form of trypsin helps liquefy secretions and loosen bronchial plugs and promotes patient cooperation.

SUMMARY AND CONCLUSIONS

Trypsin in sesame oil was effective in cases in which it was tolerated. In many patients, the local pain and induration at the injection site was severe enough to discontinue treatment.

Trypsin in buccal tablets produced soreness and in some cases ulcerations of the mouth severe enough to warrant complaints. Clinical response was minimal, producing less tenacious sputum and easier expectoration.

Trypsin aqueous gave fewer side effects and was rather well tolerated by most of the patients. This preparation did liquefy bronchial secretions and loosened bronchial plugs .

The newest pharmaceutical form of trypsin—enteric coated for oral administration —was clinically effective in pulmonary diseases, convenient to use, and obtained patient cooperation.

Our clinical experiences with the various pharmaceutical formulations of crystalline trypsin dictate the impression that trypsin aqueous and enteric coated trypsin are effective therapeutically in certain pulmonary diseases used either alone, or in combination, as we described. They seem to enhance the clinical effectiveness of antituberculosis drugs and antibiotics and thus promote more rapid clinical improvement in patient with pulmonary diseases due to infections.

ACKNOWLEDGEMENT: The various trypsin preparations were supplied by the Medical Research Department, National Drug Company, Philadelphia, Pennsylvania.

RESUMEN

La tripsina en aceite de sésamo fue efectiva en los casos que la toleraron.

En muchos enfermos el dolor local y la induración en el sitio de la inyección fue bastante severo como para obligar a la suspensión del tratamiento.

La tripsina oral en algunos casos produjo erosión y ulceraciones de la boca que fueron motivo de queja. La respuesta clinica fuá mínima produciendo esputo menos espeso y mas facil expectoración.

La tripsina acuosa dío menos efectos colaterales y fué mejor tolerada por los enfermos en su mayoría. Esta preparación produjo la liquefacción de las secreciones bronquiales y aflojó los tapones bronquiales.

La forma farmaceutica mas nueva de tripsina con capa enterica para la administración oral fué efectiva clinicamente en enfermedades pulmonares, conveniente para usarse y obtuvo la cooperación del enfermo.

Nuestra experiencia clínica con las diversas formas farmaceúticas de la tripsina cristalina conducen a la impresión de que tripsina acuosa y lade la capa enterica son efectivas en ciertas enfermedades pulmonares ya sea sola o en combinaciones como se describen. Parece que aumentan la efectividad de las drogas antituberculosis así como promueven una mejoría clínica mas rápida en los enfermos, de padecimientos pulmonares infecciosos.

RESUMÉ

La trypsine dans l'huile de sésame fut efficace dans les cas où elle a été tolérée. Chez beaucoup de malades, la douleurs locale et l'induration au point d'injection furent suffisamment graves pour qu'on cesse son emploi.

La trypsine en tablettes par la bouche produisit un endolorissement et dans certains cas des ulcérations de la bouche suffisamment graves pour justifier les reproches des malades. La réponse clinique fut faible, produisant une expectoration moins tenace et plus facile.

La trypsine en solution aqueuse donna lieu à des complications moins nombreuses, et fut plutôt mieux tolérée par la plupart des malades. Cette préparation liquéfia les sécrétions bronchiques et amollit les bouchons bronchiques.

La plus récente présentation pharmaceutique de trypsine (kératinisée pour administration orale) se montra cliniquement efficace dans les affections pulmonaires, propre à l'emploi et obtint l'approbation des malades.

Les expériences cliniques que l'auteur a poursuivies avec les différentes formules pharmaceutiques de trypsine cristallisée donne l'impression que les trypsines aqueuses et kératinisée sont efficaces du point de vue thérapeutique dans certaines affections pulmonaires, si elles sont utilisées soit seules, soit en association, comme il l'a décrit. Elles semblent augmenter l'efficacité clinique des produits antituberculeux et des antibiotiques et peuvent donc apporter une amélioration clinique plus rapide chez les malades atteints d'affections pulmonaires d'origine infectieuse.

ZUSAMMENFASSUNG

Trypsin im Sesamöl war von guter Wirksamkeit in den Fällen in denen es vertragen wurde. Bei vielen Kranken waren der örtliche Schmerz und die Induration an der Injektionstelle schwer genug, um mit der Behandlung aufzuhören.

Trypsin in buccalen Tabletten bewirkte Mundfäule und in einigen Fällen auch zu Zahnfleischgeschwüren von einem Ausmaß, daß Komplikationen zu fürchten waren. Die klinische Reaktion war nur minimal und bewirkte ein weniger zähes Sputum und dessen leichtere Entleerung.

Trypsin in wässriger Lösung ergab weniger Nebenwirkungen und wurde ziemlich gut vertragen von den meisten Patienten. Dieses Präparat verflüssigte das Bronchialsekret und löste bronchiale Pföpfe auf. Die jüngste pharmakologische Form von Trypsin-darmlösliche Tabletten zur oralen Anwendung,-war klinisch wirksam bei Lungenkrankungen, angenehm beim Gebrauch und fand auch den Beifall der Kranken.

Unsere klinischen Erfahrungen mit den verschiedenen pharmazeutischen Formen des kristallinen Trypsin legen uns den Eindruck auf, daß das wässrige Trypsin und des darmlösliche Trypsin therapeutisch bei gewissen Lungenkrankheiten von Wirksamkeit sind, sei es bei ausschliesslicher oder auch bei kombinierter Anwendung, wie es beschrieben wurde. Diese Formen des Medikamentes scheinen die klinische Wirksamkeit antituberkulöser Arzneimittel zu verstärken und so eine schnellere erkrankung die Folge von Infektionen sind.

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PERICARDIECTOMY

The cause of chronic constrictive pericarditis is still a matter of interest. Although tuberculous pericarditis was originally presumed to be the responsible cause of constrictive pericarditis, it now appears that this may be comparatively rare. Comparison of a sizable series of patients with acute pericardial effusion treated during the same time interval suggests a possible relationship between acute hemorrhagic pericarditis and chronic constrictive pericarditis. During the past ten years, 26 patients have been operated upon at the Cleveland Clinic Hospital for the surgical correction of chronic constrictive pericarditis. There has been considerable variation in technical features of the operation, but with increasing experience the trend is toward one of two basic incisions: 1) the median sternotomy (sternal-splitting) or 2) the transverse sternotomy (sternal transection). Either incision provides excellent exposure of the anterior aspect of the pericardial sac and its contents. Successful decortication is dependent upon the surgical exposure; however, other factors may be equal in significance. The most important of these is the character of the pericardial disease in the patient. The ability to establish a cleavage plane is usually dependent upon the pathologic process itself. Other reasons for failure are myocardial disease and postoperative complications.

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The Current Role of Exfoliative Cytopathology in the Routine Diagnosis of Bronchogenic Carcinoma

A Five-Year Study of 152 Consecutive, Unselected Cases*

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Although the sensitivity of exfoliative cytopathology in the diagnosis of bronchogenic carcinoma has been reported to be as low as 44 per cent,[1] most cytologists find malignant cells in the sputum or bronchial aspirates from three of every four patients with lung cancer, more or less.[2-6] Most reports contain selected series of cases, since patients who have not had cytologic examinations usually are excluded; likewise patients in whom the quantity or quality of the smears is not adequate also may be omitted. Thus it is difficult to ascertain the full role of exfoliative cytodiagnosis of carcinoma of the lung in routine hospital practice. The purpose of this study was to determine this role by a retrospective analysis.

Material and Method

The results of all types of microscopic diagnostic modalities utilized in 152 consecutive unselected and histologically proved bronchogenic carcinomas in patients admitted to the Veterans Administration Hospital at Ann Arbor, over a five-year period (1954-1959) were reviewed and tabulated. The series included six cases in which the neoplasm was an unexpected or incidental finding at necropsy thereby precluding antemortem diagnostic studies.

One hundred and twenty-six (82.9 per cent) of the patients had some form of cytologic smear examination-sputum, bronchial aspirate, or pleural fluid. Usually, multiple specimens were examined; the mean was about three specimens per patient. However, in many instances the cytologic study was limited to the examination of a single specimen. Four smears were prepared from each specimen and were processed in accordance with the standard Papanicolaou technique.

Ninety-six (63.2 per cent) of the patients were subjected to bronchoscopy; for the purpose of this study, bronchoscopy was interpreted as positive only when a histologic diagnosis of carcinoma was made by bronchial biopsy.

Eighty-nine patients (58.6 per cent) had anterior scalene lymph node biopsies, performed according to the technique of Daniels.[7] The lymph nodes were obtained from the right side when a lesion was present in the right lung or the left lower lobe; left scalene lymph node biopsies were reserved for lesions in the left upper lobe or lingular segments. The number of lymph nodes in these specimens varied from 0 to 20 with a mean of six. Histologic examinations of tissue from suspected metastases were made in 18 cases. These tissues included lymph nodes (other than scalene), liver, skin, bone, or central nervous system. Thus a total of

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TABLE 1 — MICROSCOPIC DIAGNOSIS OF 152 CONSECUTIVE UNSELECTED CASES OF HISTOLOGICALLY PROVED CARCINOMA OF THE LUNG PRIOR TO THORACOTOMY OR NECROPSY.

Cytopathology	No. patients examined	Positive		Percentage of total patients
Sputum	111	82 (73.9)		53.9
Bronchial aspirate	69	50 (72.5)		32.9
Pleural fluid	14	8 (57.1)		5.3
(Combined)	126	100 (79.0)		65.8
Bronchial biopsy	96	49 (51.0)	Per cent	32.2
Biopsy of metastasis				
Scalene lymph node biopsy	89	15 (16.9)		9.9
Others	18	13 (72.2)		8.6
(Combined)	107	28 (26.2)		18.4
Punch biopsy of lung or pleura	4	2 (50.0)		1.3

107 (70.5 per cent) patients had some form of histologic examination to demonstrate metastatic bronchogenic carcinoma.

Punch biopsy of the lung or pleura was performed on four patients.

Results

The number and percentage of positive cytologic and biopsy results are given in Table 1. One hundred (79.0 per cent) of the 126, or 65.8 per cent of the total 152 patients, who had cytologic examinations were found to have malignant cells in the smears. In contrast, only 32.2 per cent of the patients had positive bronchoscopic biopsies, although over one-half of the bronchoscopic examinations produced histologic proof of carcinoma. Less productive were the anterior scalene lymph node biopsies and other attempts to establish the presence of metastasis from primary carcinoma of the lung, since only 18.4 per cent of the patients had histologically proved metastases prior to thoracotomy or necropsy. However, when positive, these biopsies provided a criterion of inoperability. From a quantitative standpoint, punch biopsy of the lung or pleura played an insignificant diagnostic role.

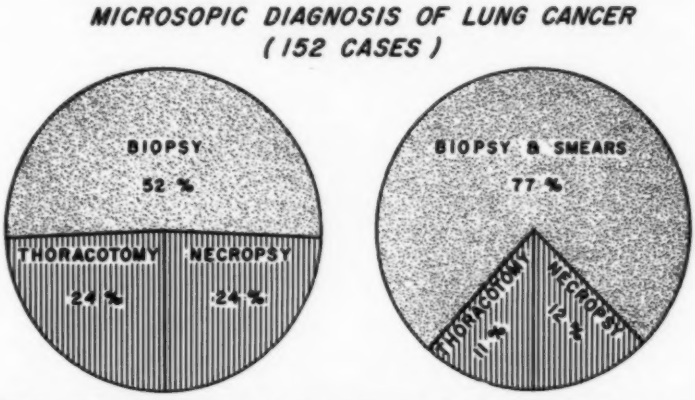

FIGURE 1: Microscopic diagnosis of lung cancer prior to thoracotomy by necropsy, by biopsy only, and by biopsy and smears.

TABLE 2 — CASES IN WHICH ONLY ONE DIAGNOSTIC MODALITY PROVIDED MICROSCOPIC EVIDENCE OF CARCINOMA PRIOR TO THORACOTOMY OR NECROPSY

	Number	Percentage of total 152 patients
Cytopathology	38	25.0
Bronchial biopsy	13	8.6
Scalene lymph node biopsy	5	3.3
Other metastases	6	3.9
Punch biopsy of pleura	1	0.7
Total	63	

The practical value of cytopathologic smear diagnosis is shown in Table 2. In 38 cases, positive smears of sputum, bronchial aspirates, or pleural fluid provided the sole microscopic evidence of lung cancer prior to thoracotomy or necropsy. This is also illustrated in Figures 1 and 2. If the cytologic results were eliminated from the diagnostic studies, only 52 per cent of the patients would have had a microscopic diagnosis prior to thoracotomy or necropsy, whereas the combined cytopathologic and histopathologic studies increased this diagnostic sensitivity to over 75 per cent (Figure 1). The contrast is even more striking in the 50 resected cases where the percentage of preoperative microscopic diagnoses was doubled by the addition of the cytologic investigations (Figure 2). Only 28 per cent of the pulmonary resections were undertaken without a preoperative microscopic diagnosis having been made.

The significance of the location of the neoplasm in the accuracy of cytologic diagnosis is given in Table 3. Positive smears were obtained from 39 of 56 (69.6 per cent) cancers in upper lobes and 29 of 35 (86.4 per cent) in lower lobes.

The sensitivity of cytologic diagnosis varied inversely with the distance of the neoplasm from the carina (Table 3) although the size of the tumor proved to be a modifying factor. Less than 50 per cent of the small peripheral carcinomas were associated with positive smears, in contrast to 14 of the 15 peripheral carcinomas which were over five centimeters in size (Table 4). On the other hand, tumor size had little influ-

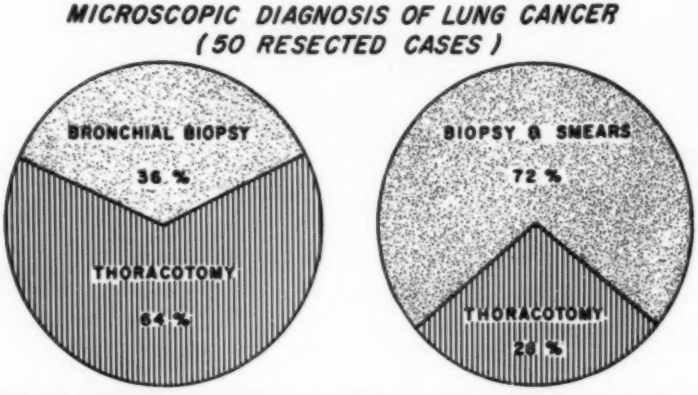

FIGURE 2: Microscopic diagnosis of resected cases of lung cancer prior to thoracotomy by biopsy only and by biopsy and smears.

TABLE 3 — SIGNIFICANCE OF TOPOGRAPHY (IN THE CYTOLOGIC DIAGNOSIS)

Location	Total	Positive	Percentage
Upper lobe	56	39	69.6
Lower lobe	35	29	86.4
Not determined	61		
	152		
Hilar (Main-stem or lobar)	55	46	83.6
Peripheral (Segmental or subpleural)	44	29	65.9
Not determined	53		
	152		

ence on the cytologic diagnosis of hilar carcinomas. In fact, the larger hilar neoplasms were detected slightly less frequently, probably because of the greater incidence of bronchial obstruction.

Discussion

The practical value of a diagnostic modality may be measured better in an unselected series such as this rather than by the determination of its sensitivity under ideal circumstances. For example, the sensitivity of bronchoscopic biopsy of visible lesions of the bronchi is high, but many lesions are not visible, or are beyond the reach of the bronchoscope, and bronchoscopy is often omitted because of roentgenographic demonstration of subpleural location of the neoplasm or because of medical or structural contraindications. Similarly, if the sensitivity of smear diagnosis of exfoliated material is determined on the basis of the number of patients with bronchogenic carcinoma who have multiple examinations of adequate specimens of sputum or bronchial aspirates, the great majority of such patients will be found to have malignant cells in the smears. Nevertheless, some patients are unable or unwilling to raise sputum, or their sputum may not include bronchial secretions.

This study indicates the great impact of exfoliative cytopathology on the routine diagnosis of bronchogenic carcinoma. The number of patients who had positive smears exceeded the combined results of all methods of histologic diagnosis, exclusive of thoracotomy and necropsy. Of greater significance is the finding that 25 per cent of the patients had positive smears as the only microscopic proof of carcinoma prior to thoracotomy or necropsy.

The review of the resectable cases is even more significant and here too the diagnostic potentialities of exfoliative cytopathology are demonstrated. In the absence of cytologic examination only about one-third (36 per cent) of the patients with resected neoplasms in this series would have had a microscopic diagnosis of carcinoma prior to operation. The examination of smears of sputum or bronchial aspirates doubled this number so that almost three-fourths (72 per cent) of the patients had proved carcinoma prior to thoracotomy.

The full potentialities of smear diagnosis were not realized in this series of patients. Twenty-six patients did not have the benefit of cytologic examination. Admittedly, in some of these cases the examination was not necessary, the diagnosis having been established by other means. However, in some instances the patients were unable to raise sputum; this failure to raise sputum occurred prior to the use of aerosol sputum induction, which has practically eliminated unsatisfactory sputum specimens.[8,9] In some instances, the patient died before specimens could be obtained. Among the 26 patients who had false negative cytologic reports, were many patients who had only one specimen examined. These incomplete cytologic studies were occasioned by misunderstanding on the part of the medical or nursing staff, death, or the establishment of diagnosis by another means.

TABLE 4 — SIGNIFICANCE OF TUMOR SIZE (IN THE CYTOLOGIC DIAGNOSIS)

Location	Total	Positive	Percentage
Hilar			
5 cm. or less	14	13	92.9
over 5 cm.	24	20	83.3
Peripheral			
5 cm. or less	25	12	48.0
over 5 cm.	15	14	93.3
Undetermined	74		
	152		

Most of the false negatives among patients who had adequate cytologic specimens were associated with small peripheral carcinomas, or hilar neoplasms with advanced bronchial stenosis.

The frequent failure to detect malignant cells in patients with small (less than five centimeters in diameter) peripheral carcinomas is disturbing, especially from the standpoint of early detection of carcinoma of the lung. Since the larger peripheral neoplasms (over five centimeters in diameter) were detected cytologically with regularity (14 of 15), it would appear that the total exfoliative surface was of considerable significance. On the other hand, the size of hilar neoplasms had relatively little effect upon the cytologic results. If there was any significance of tumor size in the case of the hilar carina, it was an inverse relationship, presumably related to bronchial stenosis associated with more advanced carcinomas.

SUMMARY

1. In 152 consecutive unselected patients with histologically proved carcinoma of the lung, including six with unsuspected neoplasms at necropsies, a microscopic diagnosis was established by exfoliative cytopathology in 100 cases. Twenty-six of the 152 patients were not examined by the smear technique and 26 had negative smears.

2. A positive cytologic diagnosis was made more frequently (65.8 per cent) than a prethoracotomy histologic diagnosis (52.0 per cent) using all types of standard biopsy methods.

3. In 25 per cent of the patients, exfoliative cytopathology provided the only microscopic evidence of carcinoma prior to thoracotomy or necropsy.

4. Exfoliative cytodiagnosis increased the prethoracotomy microscopic diagnosis of carcinoma of the lung from 36 per cent to 72 per cent in 50 patients whose carcinomas were resected.

5. The cytologic diagnosis of carcinoma of lower lobes was 16.8 per cent greater than that of upper lobes. The frequency of malignant cells in sputum or bronchial aspirates varied inversely with the distance of the neoplasm from the carina, except for peripheral tumors over five centimeters in size which were detected as frequently as were those in the hilar areas.

RESUMEN

1. Entre 152 enfermos no escogidos, con carcinoma pulmonar demostrado histológicamente, incluyendo seis con neoplasias no sospechosas hasta la necropsia, se sentó un diagnóstico por la citopatología exfoliativa en 100 casos. Veintiseis de los 152 enfermos no se examinaron la técnica del frotis y 26 tuviero frotis negativos.

2. El diagnóstico citológico positivo se hizo mas frecuente (65.8 por ciento) que el diagnóstico histológico antes de la toracotomía (52 por ciento) usando todas las formas de biopsia.

3. En 25 por ciento de los enfermos la citología exfoliativa proporcionó la única evidencia microscópica antes de la toracotomía o necropsia.

4. El citodiagnóstico exfoliativo aumentó el número de diagnósticos microscópicos antes de la toracotomía por carcinoma del pulmón de 36 por ciento a 72 por ciento en 50 enfermos cuyo carcinoma se resecó.

5. El diagnóstico citológico del carcinoma de los lóbulos inferiores fué 16.8 por ciento mayor que el de los lóbulos superiores.

La frequencia de celdillas malignas en el esputo o productos de aspiración bronquial varió en proporción inversa con la distancia de la carina, excepto para los tumores periféricos de mas de 5 cms. que se revelaron tan frecuentemente como los hiliares.

RESUMÉ

1. Pour 152 malades non sélectionnés chez lesquels un cancer pulmonaire a été mis en évidence par l'histologie, y compris six cas de néoplasies insoupçonnées découvertes à l'autopsie, le diagnostic microscopique fut établi par la cytologie dans 100 cas. 26 des 152 malades ne furent pas examinés selon la technique des frottis, et 26 eurent des frottis négatifs.

2. Le diagnostic cytologique a été plus fréquemment positif (65.8%) que le diagnostic histologique avant thoracotomie (52%) tous les types de méthodes biopsiques classiques ayant été utilisés.

3. Chez 25% des malades, la cytologie fournit la seule preuve microscopique de cancer avant la thoracotomie ou l'autopsie.

4. Le cytodiagnostic a permis que le diagnostic microscopique avant thoracotomie pour cancer pulmonaire puisse être fait dans une proportion qui a passé de 36 à 72% chez 50 malades ayant subi une exérèse pour cancer.

5. Le diagnostic cytologique de cancer des lobes inférieurs se montra plus élevé de 16.8% que celui des lobes supérieurs. La fréquence des cellules malignes dans l'expectoration ou l'aspiration bronchique varia en raison inversa de la distance du néoplasme à la carène, sauf pour les tumeurs périphériques de plus de cinq centimètres qui furent détectées aussi fréquemment que le furent celles des zones hilaires.

ZUSAMMENFASSUNG

1. Bei 152 aufeinanderfolgenden gut ausgewählten Fällen von histologisch gesichertem Lungencarzinom einschliesslich Testfällen von nicht vermutetem Neoplasma bei der Sektion, wurde eine mikroskopische Diagnose durch pathologisch-histologische Untersuchung abgestoßener Zellen in 100 Fällen gestellt. 26 der 152 Kranken wurden nicht mit der Ausstrichtechnik untersucht, und 26 hatten negative Ausstriche.

2. Eine positive cytologische Diagnose wurde häufiger gestellt (65.8%), als eine der Thorakotomie vorausgehende histologische Diagnose (52.0%), unter Verwendung aller bioptischen Standardmethoden.

3. Bei 25% der Kranken erwies sich die Cyto-Pathologie vor der Thorakotomie oder Autopsie als der einzige mikroskopische Beweis für ein Carzinom.

4. Die exfoliative Cyto-Diagnostik führte zu einer Erhähung der präoperativen mikroskopischen Carzinom-Diagnosen der Lunge con 36% bis auf 72% bei 50 Kranken, deren Carzinome reseziert wurden.

5. Die cytologische Carzinom-Diagnose der Unterlappen war 16.8% größer als diejenige der Oberlappen. Die Häufigkeit bösartiger Fälle im Sputum oder aspirierten Bronchialsekret schwankte im umgekehrten Verhältnis zur Entfernung der Feschwulst von der Carina, ausgenommen periphere Tumoren von mehr als 5 cm Größe, die ebenso häufig entdeckt wurden, wie diejenigen im Hilusbereich.

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UNEXPECTED DEATH IN BRONCHIAL ASTHMA: A WARNING SIGN WITH A CLINICOPATHOLOGIC CORRELATION

At the necropsy table, the clinical picture can be readily reconstructed. The progressive obliteration of the minor pulmonary radicles by mucus plugs leads to a decrease in the number of functioning alveoli, resulting in compensatory dyspnea. As the muscular and cartilaginous subsegmental and segmental bronchi are occluded, wheezing and breath sounds decrease, since air can neither enter nor leave the blocked channels. This process continues to involve more and more of the lung, so that the ventilatory capacity is severely reduced, and when a strategic bronchus is finally occluded, sudden asphyxia and death ensue.

The clinical picture of decreased wheezing, increased dyspnea, and decreased breath sounds indicates a poor prognosis, and calls for a review of the therapy given. The following suggestions are offered: 1) do not oversedate the asthmatic patient; 2) encourage coughing and give expectorant help; 3) use oxygen only if necessary, and then only in conjunction with a wetting agent; 4) ensure adequate hydration.

If the patient's condition does not show rapid improvement, or if there is continued deterioration, then general anesthesia, preferably with ether, should be given and bronchoscopy with diligent aspiration performed. This may be life-saving.

O'Brien, M. M., and Ferguson, M. J.: "Unexpected Death in Bronchial Asthma: A Warning Sign with a Clinicopathologic Correlation," *Ann. Int. Med.*, 53:1162, 1960.

The Effect of Cationic Resins and of Chelating Agents in Media for Cultivation of M. Tuberculosis on Membrane Filters

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A cogent reason for using the membrane filter in the primary isolation of *Mycobacterium tuberculosis* directly from the human host is that with one filtration a two-fold objective is attained; by its use, most of the tubercle organisms in the specimen are collected on one plane freed of other material, and that the membrane itself serves as a base for growth *in situ* in media and by modes that favor a more rapid initiation of growth of the tubercle bacilli than by more conventional technics.

This report recapitulates briefly a method by which most of the tubercle organisms in a sputum sample may be collected by filtration on membranes freed of sputum debris, and describes two media augmented by cationic resins and chelating agents which initiated early growth of *M. tuberculosis* in primary cultures more rapidly than occurred in control media, Lowenstein-Jensen slants.

Materials and Methods

A. *Equipment*

Microfilter, Tietz, T2, mounted by stopper in a liter Pyrex flask without use of the threaded chamber.** Membrane filters, T2, 20 mm. diameter.** Chromatographic paper No. 470A, cut in strips 5 x 0.5 in.** Flat, oval test tubes, 15 x 2.5 cm. No. 78270† (Fig. 1). Standard, stackable, Pyrex baking dishes, 10 x 12 in. Dropping pipette; spinal puncture needle, cut off squarely at the tip, attached to a glass adapter and rubber bulb.

B. *Materials*

Enzyme: Pangestin,® a 4 per cent suspension in distilled water, centrifuged, the supernate decanted and to it an equal amount of 12 per cent magnesium sulfate added. This stock solution was stored in 25 ml. amounts in the deep freeze.

Decontaminants: Stock solution of 1:500 aqueous solution of Zephiran.

Polymyxin-b-sulfate: Stock solution of 10,000 units/ml. in distilled water made weekly.

Hydrocarbons: n-octane or pentane.‡

Cationic exchange resin: Duolite C-3 (H+)‡‡ and the same resin in Mg++ form.

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*Imperial Valley Tuberculosis Sanatorium. This work was supported by a generous grant from the Imperial County Tuberculosis and Health Association, El Centro, California.

**Micro filter, membrane filters, chromatographic paper from Carl Schleicher and Schuell Co., Keene, New Hampshire.

†A. S. Aloe and Co., St. Louis, Missouri.

®Pangestin, Difco Laboratories, Inc., Detroit, Michigan.

††Zephiran (alkyl-dimethyl-benzyl ammonium chloride), Winthrop-Stearns, Inc., New York, New York.

‡n-octane, pentane, Eastman Kodak Company, Distillation Products Division, Rochester, New York.

Chelating agents: Kojic acid.§

C. *Outdated bank blood or human plasma, lyophilized, without preservatives*§§

Methods

A. *Preparation of sputum*

The method of sputum preparation for filtration, previously described,[1] is essentially a double concentration method of the tubercle organisms. The sputum sample, digested to the fluid state by incubating (or shaking) with 4 per cent Pangestin, polymyxin-b-sulfate, 100 units/ml. of sample and 1:1000 (total conc.) of Zephiran was centrifuged, and the supernate replaced quantitatively with distilled water and 2 to 4 ml. n-octane or pentane. After mechanical shaking for five minutes, the tube was set upright to permit separation of the fluid phases. By this means, most of the fatty tubercle organisms passed into the hydrocarbon layer, freed of sputum debris. This hydrocarbon layer was skimmed by pipette *to the junction line* (where most of the organisms were) and transferred, drop by drop, to the membrane disk under partial vacuum mounted in the filter.

The hydrocarbon was routinely transferred at 10-5-2 drops per disk (3 per tube) which, in turn, were mounted on a blotting paper strip soaked in the test medium (usually 3-4 ml. per tube). Tubes were left loosely stoppered in the incubator for several hours to permit complete evaporation of the hydrocarbon, then sealed by dipping the cotton plug in a hot paraffin mixture (⅔ paraffin, ⅓ vaseline) which effectively prevented gas or moisture escape. The tubes were laid flat in Pyrex dishes which were stacked for incubation. Since the tubes have flat parallel sides and were firmly sealed, they could be examined repeatedly without disturbing the disks with a stereoscopic microscope, by means of a pencil beam of light cast parallel to the plane of culture.

At times, the uppermost disk in a tube was withdrawn by sterile forceps and laid culture-side down on a slide with firm pressure applied. The growth on the disk transferred to the slide, when stained, presented a mirror image of the original growth. By this means, even non-visible growth could be demonstrated at an early stage in a small area in the slide easily scanned microscopically. The remaining membranes in the tube were re-incubated for further growth.

B. *Sterilization of membranes*

The small membranes were most easily sterilized by boiling immediately before use in distilled water. They are not grid marked; therefore, a packet before boiling was riffled sideways and the edges marked with strokes of an indelible pencil so that, when picked from the water with sterile forceps, the disks were placed on the filter, film-side up.

C. *Titration of cationic resin*

Various lots of cationic resins differ in their H+ binding capacity, and each lot must be titrated before use on a wt./vol. basis with citrated

‡‡Duolite C-3 (H+), Chemical Process Company, Redwood, California. Generous samples of this resin and in the Mg.++ form were furnished for this work by Dr. I. Forest Huddleson, Michigan State University, East Lansing, Michigan.

§Generously sent by Sigma Chemical Company, St. Louis, Missouri.

§§Courtland Laboratories, Los Angeles, California.

blood. As Huddleson recommends[2,3] for Duolite-C-3 (H+) for example, which is furnished in a dry-bead form, the colloidal dust was removed by washing and the resin dried at low heat for 24 hours. To 0.2, 0.3, 0.4, 0.5 gm. placed in separate small beakers was added 10 ml. of blood per beaker. After 30 minutes, the pH of the blood samples were tested with a glass electrode, to determine the quantity of resin required to reduce the pH of the blood to 5.9-6.2. This aliquot of resin (or multiples) was transferred to 50-100 ml. cotton stoppered bottles and autoclaved. After sterilization, the cotton plugs were replaced with rubber stoppers and the bottles stored for use in the basic preparation of media for test.

Outdated bank blood. The blood was allowed to settle in the cold and only the fluid portion with a small admixture of red cells was used. The settled red cells were discarded. Adjuvants were added as indicated in the text.

The data in the tables are representative of several similar experiments and indicate the useful data within a range of trials. Additional details of technic are given in the text as required.

Results

One of the most valued features of membrane filter use is that, with an adequate medium, discrete colonial growth is visible earlier than by other cultural methods. For diagnostic purposes, the information sought is rarely quantitative, but is definitive—and in the shortest possible time. Hence, any medium in which bacterial lag is reduced and active cell multiplication re-established is preferable.

The recent trend in tuberculosis diagnostic work is the use of whole blood or bovine serum in many cultural combinations, for both fluids furnish preformed a medium that the most exacting artificial formulation cannot duplicate. For most laboratories or hospitals in this country concerned with tuberculosis diagnostic culture, human plasma or outdated bank blood is more readily obtainable, commercially or otherwise, than is bovine serum.

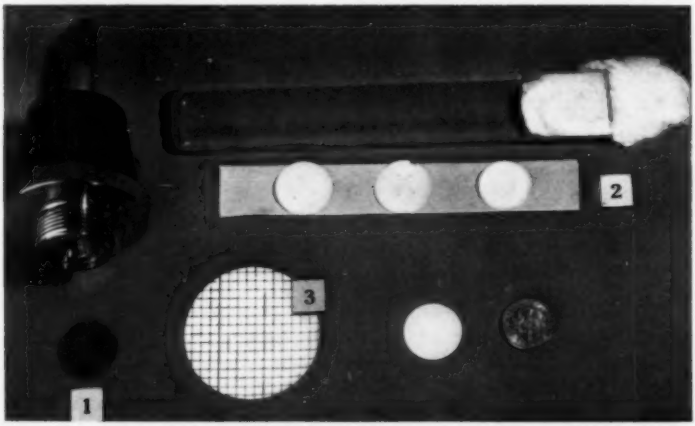

FIGURE 1: (1) Tietz, T2 micro-filter with membrane supporting disk. (2) Flat tube with withdrawn culture assembly of micro-membranes after incubation—2 weeks. (3) Comparison of standard membrane, 47 mm. with micro-membranes used.

Lyophilized, irradiated human plasma

This product as commercially furnished has no preservatives. Reconstituted to volume with distilled water (pH 7.0) and used as medium human plasma produced a slower growth than occurred on control medium. The ensuing trials with additives were made with a two-fold increment of dilutions. When favorable growth was noted with any combination, that ingredient was tested repeatedly by narrowing the concentration range to fix the point of maximum growth with minimum concentration. The inocula were derived from freshly processed sputa in pentane (or n-octane) concentrations showing acid-fast rods by smear. The number of organisms per drop of inocula, therefore, varied from experiment to experiment. The data shown in the composite tables are the final resultant figures from repeated experiments in each category. Growth of inocula on Lowenstein-Jensen slants were used as controls.

Human plasma and phosphoric acid

The use of phosphoric acid was suggested by Winder and Denneny[4] who analyzed the metaphosphate metabolism of several strains of mycobacteria.

Phosphoric acid was used in a range from 50 μg/ml. to 1000 μg/ml. The effective range lay between 100-200 μg/ml. and the final figure used for later tests was 150 μg/ml. This amount reduced the pH of the plasma from 7.0 to approximately 6.4. The reduction in lag time compared with control media was about two weeks. When 2 per cent glycerol was added to human plasma and 150 μg/ml. phosphoric acid, growth was further moderately stimulated as shown in Table 1. Other acids similarly tested, glutamic acid, pyruvic acid, citric acid, were without observable effect either with or without glycerol.

Human plasma and kojic acid

Kojic acid (3 hydroxy-6-hydoxymethyl ∝ pyrone) was selected for trial as a widely used representative of a class of compounds (3 hydroxy ∝ pyrones) known to have growth-stimulating action in biological systems,[5] not only because the stimulating effect has been narrowed by some workers to its chelating action, but because its chelating stability constant is high for such ions as Mn++, Ca++ and Mg++. Here the effective

TABLE 1—SUMMARY TABLE OF STIMULATORY EFFECT OF ADDITIVES WITH HUMAN PLASMA ON GROWTH OF *M. TUBERCULOSIS** ON MEMBRANE FILTERS

Additive and Conc.	Effective Concentration		Range Inc. Time - Weeks	
	Range	Optimum		L-J-
	Human Plasma — 2 per cent Glycerol		Test	Control
Phosphoric Acid μg./ml.	100-200 μg.	150 μg.	3-4	4.5-6
Kojic Acid μg./ml.	50-400 μg.	350 μg.	3.5-4.5	4.5-6
Phosphoric Acid μg./ml. and Kojic Acid μg./ml.	100-200 μg.	180 μg.	2-3.5	4.5-6
	100-450 μg.	300 μg.		

*Ioculum: MFs-2-5-10 drops pentane conc. sputum. Control medium 5-10 drops pentane conc. sputum.

range was fairly wide, ranging from 50 μg/ml. to 400 μg/ml. (Table 1). When 350 μg/ml. was used, the pH dropped from 7.0 to approximately 6.8. Growth was also moderately increased when 2 per cent glycerol was added and the lag time dropped about two weeks as shown in Table 1. Inspection of the cultures were made weekly with the aid of a stereomicroscope and grazing light which threw even minute colonies visually into high relief. Later, immediately after inoculation, examinations were made semi-weekly and from one of a pair of tubed membranes, the uppermost disk was withdrawn aseptically for a stained contact impression of growth. By this means, even non-visible growth could be demonstrated and confirmed by later growth of the remaining membranes. Again, pyruvic, glutamic or citric acids, added to kojic acid and glycerol with the plasma base had no observable effect on growth of tubercle organisms.

Human plasma, kojic acid and phosphoric acid

When kojic acid and phosphoric acid were combined with plasma and 2 per cent glycerol, a very definite acceleration of growth resulted that suggested potentiation. In repeated trials, with the concentration of one acid held constant and the other increased serially and vice versa (Table 2) the most rapid growth was with the combination of kojic acid 300 μg/ml. and phosphoric acid 180 μg/ml. with 2 per cent glycerol, reducing the pH to 6.2 and the lag time from 5-6 weeks of the control growth to 2 to 3 weeks on plasma medium on membrane filters for the development of fuly visible colonies. By the contact impression method, beginning growth could be demonstrated by acid-fast stain as early as 8 to 10 days following inoculation.

The results with this combination of acids suggests several interpretations that are not mutually exclusive; a potentiating effect of acid upon the metabolism of the other, possibly through the vicinal 3-hydroxy and ketone oxygens of kojic acid, the structure of which is known to account for this acid's chelating action[5] coupled with a possible specific chelation with Mg++ ions which are necessary for the functioning of the natural antimicrobial system and thus a reduction of this inhibitory action (although more complex reactions have been postulated for post-chelation effects as discussed later). Associated with this is the release of carbon dioxide immediately from plasma in an acid medium and the continu-

TABLE 2—SUMMARY TABLE OF RESULTS WITH COMBINED USE OF KOJIC ACID AND PHOSPHORIC ACID WITH HUMAN PLASMA ON GROWTH OF *M. TUBERCULOSIS* ON MEMBRANE FILTERS

Concentration of Additives	Incubation Range					Weeks
	Phosphoric Acid - μg./ml.					L. J.
Kojic Acid μg./ml.	120	140	160	180	200	Control
300	3	2.5-3.5	2.5-3	2-2.5	2-3	4.5-6
	Kojic Acid - μg./ml.					L. J.
Phosphoric Acid μg./ml.	200	250	300	350	400	Control
180	3-3.5	3-3.5	2-2.5	2-3	3-3.5	4.5-6

Inoculum: As in preceding Table 1

ing formation of carbon dioxide from glycerol, acting as a potent metabolic stimulant.

Outdated bank blood with cationic resins

Huddleson[2,3] recently demonstrated that undiluted whole blood supported rapid growth of the fastidious brucellae (and many other gram-negative speciese) if a cationic resin in the H+ cycle and sodium citrate alone were used. Then, by adding an M++ exchange resin, the gram-positive organisms tested also grew abundantly in the same medium. The rapid exchange of H+ ions with the metallic ions of the soluble salts in the fluid quickly reduced the pH of the blood which, with the additional chelating action of the sodium citrate present not only inactivated the normally occurring antimicrobial factors found in blood, but stimulated the production of carbon dioxide for those organisms requiring it for growth. By this means, Huddleson eliminated entirely the cultural media usually added to blood in order to utilize the full nutritive value of blood alone.

The technic outlined in (3) was changed by substituting outdated bank blood (4 weeks old, with ACD-B)* for fresh human blood and no additional sodium citrate was used. The Duolite C-3 H+ resin and the Mg.++ exchange resin were titrated together in the blood to the pH 6.0 end point in 30 minutes and used with 2 per cent glycerol.

Medium thus prepared and used with filtered tubercle organisms on membranes produced visible growth in two and one half to three weeks compared with control growth in 4 to 5 weeks. An addition of 100 μg/ml. of phosphoric acid to the above medium reduced the pH to 5.7-5.8 and had a perceptible stimulating effect on growth, Table 3. In several experiments with this medium, the growth was visible in two weeks, and by contact impression, stained, could be identified as *M. tuberculosis* growth in one week. Thus, with these two media, growth of concentrated tubercle organisms, after the described processing procedure, may be accurately identified in 2 to 3 weeks following inoculation.

Discussion

The classical method of studying bacterial nutrition is by the use of a minimal mineral medium to which test materials are added, one by one, in order to appraise their effect on the *in vitro* growth of bacteria. By this technic, a vast body of data for a wide variety of organisms has advanced knowledge of synthetic pathways during anabolism, of growth control mechanisms, of specific catalysts and, of late, the biochemical dynamics of cell surface phenomena; the identification of specific transport systems (permeases) by which organic substances pass into the microbial cell (Monod,[6] Mitchell,[7] Rothstein[8]).

*ACD-B—1.32 per cent trisodium citrate, 0.48 per cent citric acid, 1.47 per cent dextrose—25 ml./100 ml. blood.

TABLE 3—BANK BLOOD WITH SERIAL ADDITIVES AS MEDIUM FOR GROWTH OF *M. TUBERCULOSIS* ON MEMBRANE FILTERS

Bank Blood (ACD) Used With					Lowenstein Jensen Control
Alone +	2 per cent Glycerol +	Duolite C-3 .45 gm./ 10 ml. +	Mg++ resin .05 gm./ 10 ml. +	Phosphoric Acid 100 μg./ml.	
Range		Incubation Time			Weeks
<5-6	<4.5-6	3-4	2.5-3	2-3	4-6

Inoculum: As in Table 1.

Nevertheless, it is clear that this wealth of biochemical data throws little light on the metabolism of a pathogen growing *in vivo*—on the nature of the micro-environment within the *living* phagocyte, or in the inflammatory site marked by a high glycolysis, of high carbon dioxide and of low oxygen tension, of high concentrations of organic and fatty acids and of low pH in which the pathogen survives—and grows (Dubos[9]). Although *M. tuberculosis* adapted to *in vitro* growth shows a surprising range of metabolic activities on very simple media (Darzins[10]), the pronounced "lag" which almost invariably ensues on primary transfer of the tubercle bacillus from the infected human host to laboratory media is a clear indication of the metabolic challenge presented the organism in the change from one environment to the other. Some understanding of the actual difference between *in vitro* and *in vivo* metabolism of a single strain of *M. tuberculosis* is furnished by the careful studies of Segal and Bloch.[11] Tubercle bacilli collected from heavily infected mouse lungs used, without intermediate culture, in parallel tests with the same strain grown only *in vitro* showed marked difference in response to glucose, glycerol, lactic acid, sodium pyruvate, sodium benzoate, benzaldehyde, sodium salicylate, n-heptanoic, octanoic, and oleic acids. These differences considered together, firmly establish the fact that tubercle bacilli in their natural infectious state are dissimilar to those grown in artificial medium.[11]

Similar convictions have been in the minds of many investigators who used whole blood, bovine or human serum undiluted or diluted with a great variety of other ingredients to nullify the well known effect of the antimicrobial system in blood. Following the work of Pillemer and colleagues,[12] who identified and described the "properdin" system (complement: properdin: Mg++) as a non-specific antimicrobial system against gram-negative bacteria, it remained for Huddleson[2,3] to discard the "other ingredients" and to demonstrate clearly that whole blood is an excellent culture medium used undiluted if augmented only with a cationic resin in the hydrogen cycle and sodium citrate. For those bacteria requiring Mg++ for growth, which includes the tubercle bacillus, the addition of an Mg++ exchange resin to the *acidic* medium does not reactivate the antibacterial action, but does permit excellent growth of the test organisms.

Relevant to this characteristic of the medium is the specific requirement of the tubercle organisms during growth for carbon dioxide. Long and colleagues[14] have now demonstrated by exacting isotopic technics the site of fixation and incorporation of carbon dioxide during growth.

Although whole blood or plasma cannot duplicate the complex and changing conditions in living tissue, both natural fluids furnish the necessary minerals, organic moieties, biocatalysts, and vitamins required for growth of *M. tuberculosis* in a balanced ratio. Both fluids are readily obtained and stored by most laboratories, and may be completed as media at the time of use by the simple addition of three ingredients—a cationic resin in the H+ cycle, the same resin in the Mg++ form, a chelate and glycerol.

It is probable that the early resumption of growth (confirmed for *M. tuberculosis*) is due in part to the disruption of the natural antibacterial system by chelation of the Mg++ portion of the triad by cationic resins and/or other chelates. The related quick fall in pH at the same time releases carbon dioxide from blood or serum carbonates for *immediate* use, more particularly since biotin, which is a co-enzyme for the assimilation of carbon dioxide, is present in adequate amount in both fluids. The presence of glycerol continues the production of exogenous and eventually endogenous carbon dioxide for continued growth. It is also probable that the full explanation for this result will be far more detailed, particularly in the case of kojic acid used with phosphoric acid and plasma. Aside from the postulated blocking effect of kojic acid on the properdin system by combining with Mg++, other effects in varied biologic experiments have been offered: it may transport a metal ion in non-toxic form across cell barriers impermeable to the ionic form, or by forming a soluble chelate with a stability constant such that the metal ion is yielded up only to cell enzymes or carriers which it activates specifically.[5] The results also suggest that the phosphorus metabolism is interrelated, but in what way can only be inferred from other published reports. If it can be shown that kojic acid by chelating with Mg++ can also serve as an Mg++ carrier in cation transport and that there is a correlation with phosphate movement, the growth acceleration of *M. tuberculosis* noted here will have a substantial basis.

The various cultural results herein reported are indicative only, but clearly show that the practice, initiated by Huddleson, of using cationic resins and chelating agents to serve a double or triple purpose is a method that may be usefully extended with many possible combinations by those interested in obtaining the full nutritive value of a quickly constituted blood or plasma medium for the culture of *M. tuberculosis*.

Finally, the membrane filter- blotting paper-sealed tube method of incubation takes advantage of the favorable features of liquid cultures and avoids their disadvantages: overgrowth by contamination, poor aeration and non-recognizable early growth. A single organism has a limited autonomy as a biologic unit; its continued growth depends on its successful adaptation to its needs of the immediate micro environment. Every organism impinged on the membrane is bathed constantly in a thin film of fluid which is constantly renewed by capillarity, and at the same instant it is exposed to a water saturated gas phase. This latter aspect duplicates the desirable features

of solid media as well, and to no small extent aids in the reduction of the lag period of renewed growth.

SUMMARY

The growth of tubercle organisms, concentrated from sputa, may be markedly accelerated by incubation on micromembrane filters in flat, closed tubes on media based on lyophilized human plasma and a chelating agent, kojic acid; or on outdated bank blood augmented with a cationic acidic resin and associated magnesium exchange resin with sodium citrate. As quick energy sources for both media, glycerol and phosphoric acid were used.

RESUMEN

El crecimiento de los bacilos tubèrculosos concentrados de los esputos puede acelerarse no tablemente por la incubación en filtros de micromembrana en plano, en tubos cerrados sobre medios basados en plasma humano liofilizado y con un agente quelatante, acido kojico; en sangre de banco pasada de tiempo aumentada con una resina acida catiónica y asociada con resina megnésica de recambio con citrato de sodio. Como fuentes rápidas de energía se usan el glicerol y el acido fosfórico.

RESUMÉ

La crossance des bacilles tuberculeux, recueillis dans l'expectoration, peut être considérablement accélérée par l'incubation sur des filtres à micro-membrane dans des tubes plats, fermés, sur les milieux composés de plasma humain lyophilisé, et d'un agent chélateur; ou sur un milieu au sang augmenté d'une résine cationique acide, et associé à une résine au magnesium avec du citrate de soude. Le glycérol et l'acide phosphorique furent uilisés comme sources d'énergie rapide pour les deux milieux.

ZUSAMMENFASSUNG

Das kulturelle Wachstum von Tuberkelzazillen, die aus dem Sputum gewonnen wurden, kann beträchtlich beschleunigt werden durch Inkubation auf Mikro-Membran-Filtern im flachen, geschlossenen Röhrchen auf Nährboden, die als Grundlage gelöstes menschliches Plasma und einen gelierenden Stoff z.B. Pyron haben; es läßt sich auch überaltertes Blut einer Blutbank verwenden unter Zusatz einer kationischen Harzsäure in Verbindung mit Magnesium anstelle des Harzes mit Natriumcitrat. Als rasche Energiequelle für beide Nährböden diente Glycerol und Phosphorsäure.

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Experimental Intrabronchial Administration of Neomycin in Man and Animals

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Ten years ago, Waksman and Lechevalier[1] demonstrated the important antibiotic action of neomycin against the Koch bacillus. The effect of neomycin is even greater than that of streptomycin.

Rake, Hobby and Donovick[2] have also demonstrated the antibiotic effect of neomycin in experimental tuberculosis.

Because of its toxicity, Grumbach and Rist[3] considered that parenteral neomycin injection was dangerous. However, Dumon and Courtreux[4] have shown that the blood concentration is minimal (injection of 0.33 gm. gives a maximum blood level of 1.6 microgram/ml.) afterintrabronchial administration. These workers describe good clinical results with toxic side effects following intrabronchial application.

Previous investigations have shown that when streptomycin and oxytetracycline are administered intrabronchially, their pulmonary concentration is much higher for much longer periods than the level obtained after parenteral administration with the same dose.[5]

Therapeutic concentrations of chlortetracycline, tetracycline, and penicillin are maintained for only five to six hours after administration. The pulmonary tissue concentration of erythromycin, and hydrazide (INH), as well as sulfathiazole, immediately after intrabronchial, is similar to the low content found after parenteral or oral application.[6] This is indicative of a higher diffusion rate from the point of application.

In order to study this application method, for neomycin, we administered it both intrabronchially and parenterally in patients, and intratracheally in guinea pigs and rabbits. Intrabronchial administration was effected by means of catgut tubes, since aerosols gave less satisfactory results. The pulmonary tissue concentration of all the subjects was determined after various time intervals.

Materials and Methods

A series of 18 patients was given intramuscular injections of neomycin (250 mg. per 60 kg. body weight). Another group of patients was given the same neomycin dosage intrabronchially by means of Metras catgut tubes. After neomycin administration, the entire group of 36 patients underwent pulmonary resection after varying time intervals.

Neomycin was administered to 110 guinea pigs and 14 rabbits intramuscularly or by intrapulmonary (tracheal) route. Animals from each group were sacrificed and their lungs examined at various time intervals after application.

The concentration of Neomycin in the pulmonary tissue has been determined by the method described in 1959.[6]

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TABLE 1—PULMONARY CONCENTRATION OF NEOMYCIN AFTER VARIOUS ROUTES OF APPLICATION

Man

	4 hours			24 hours		
	Min.	Med.	Max.	Min.	Med.	Max.
I.B.	780γ	1048γ	1360γ	24γ	36γ	48γ
I.M.	1.5γ	2γ	4γ	0	0	0

Guinea Pigs

	3 hours			6 hours			12 hours			24 hours		
	Min.	Med.	Max.	Min.	Med.	Max.	Min.	Med.	Max.	Min.	Med.	Max.
I.T.	412γ	512γ	760γ	190γ	212γ	320γ	96γ	100γ	112γ	24γ	28γ	32γ
I.M.	2γ	4.6γ	12γ	2γ	4γ	8γ	0	1γ	1γ	0	0	0

Rabbits

	3 hours			6 hours			12 hours			24 hours		
	Min.	Med.	Max.	Min.	Med.	Max.	Min.	Med.	Max.	Min.	Med.	Max.
I.T.	1112γ	1248γ	1400γ	580γ	624γ	860γ	124γ	136γ	248γ	24γ	36γ	48γ
I.M.	2γ	2.6γ	6γ	1γ	2γ	3γ	0	0.5γ	1γ	0	0.5γ	1γ

I.B.=intrabronchial application; I.T.=intratracheal application; I.M.=intramuscular injection. Min.=minimum concentration; Med.=medium concentration; Max.=maximum concentration.

The results of the observations on 36 patients, 220 guinea pigs and 28 rabbits have been arranged in the following tables.

Results

The table based upon results in patients demonstrates that pulmonary neomycin concentration is greater after intrabronchial administration than after parenteral administration. Neomycin pulmonary concentration three hours after intrabronchial application was 1300 microgram/ml. which is 700 times greater than the pulmonary concentration three hours after parenteral injection. An effective antibiotic concentration of 30 to 40 microgram/ml. was still present 24 hours after intrabronchial application. The animal experiments completely confirm the results obtained with humans.

Since neomycin is relatively toxic when administered parenterally, it has been discarded in ordinary practice in spite of the fact that it is a powerful antituberculosis antibiotic with a wide spectrum. Blood levels of neomycin after intrabronchial administration are very low (Table 1), explaining the high tolerance of it even during prolonged treatment (daily, for over four months).

SUMMARY

Neomycin was administered to 36 patients, 220 guinea pigs and 28 rabbits either intrabronchially or parenterally and the pulmonary neomycin concentration was determined bacteriologically. Those who received the intrabronchial administration showed a pulmonary neomycin concentration after three hours 700 times higher than those which received parenteral injection. Concentration of 1360 mcg./ml. in the pulmonary tissue were found four hours after intrabronchial application. After 24 hours, the level was 40 mcg./ml. Therefore, intrabronchial administration of neomycin is advisable in neomycin-sensitive pulmonary infections.

RESUMEN

Se administró neomicina a 36 enfermos, a 220 cuyes y a 28 conejos, ya sea intrabronquial o parenteralmente y se determinaron las concentraciones de la neomicina bacteriológicamente. Los que recibieron la droga intrabronquial, mostraron concentraciones de neomicina pulmonar después de 3 horas, 700 veces mayor que los que la

recibieron parenteralmente. La concentración de 1360 microgramos/ml. en el tejido pulmonar se encontraron cuatro horas después de la aplicación intrabronquial. Después de 24 horas, el nivel fué de 40 micro gr./ml. Por tanto, la administración intrabronquial de neomicina es aconsejable en las infecciones pulmonares que sean sensibles a esa droga.

RESUMÉ

La neomycine fut administrée chez malades, 220 cobayes et 28 lapins soit par voie intrabronchique, soit par voie parentérale, et la concentration pulmonaire de néomycine fut déterminée bactériologiquement. Ceux qui reçurent une administration intrabronchique montrèrent une concentration pulmonaire en néomycine après trois heures 700 fois plus élévée que ceux qui reçurent une injection parentérale. Des concentrations de 1.360 mcg. par ml. de tissu pulmonaire furent trouvées quatre heures après application intrabronchique. Après 24 heures le taux fut de 40 mcg. par ml. Donc l'administration intrabronchique de néomycine est souhaitable dans les infections pulmonaires sensibles à ce produit.

ZUSAMMENFASSUNG

36 Patienten, 220 Meerschweinchen und 28 Kaninchen erhielten entweder intrabronchial oder parenteral Neomycin, dessen pulmonale Konzentration bakteriologisch bestimmt wurde. Bei intrabronchialer Zufuhr ergab sich nach 3 Stunden eine pulmonale Neomycin-Konzentration, die 700 mal höher war als nach parenteraler Injektion. 3 Stunden nach der intrabronchialen Applikation fanden sich Konzentrationen von 1360 mcg./ml. Lungengewebe. Nach 24 Stunden war die Konzentration 40 mcg./ml. Deshalb wird zur intrabronchialen Verabreichung von Neomycin geraten bei neomycinsensiblen Lungeninfektionen.

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RESPIRATORY DISTRESS IN THE NEWBORN

Eighty-five newborn and 36 adult rats subjected to laboratory procedures designed to stimulate adverse prenatal influences showed difficulties and developed pulmonary lesions similar to those seen in infants of respiratory distress. The miliary atelectasis seen in the experimental animals may be the result of an interplay of complex mechanical, neural and most important of all, obstructive influences. The miliary atelectasis may be associated with a reversion to the fetal circulatory pattern which, with other factors, result in flooding of the pulmonary capillary bed. Increased pulmonary blood volume and capillary pressure are reflected in engorgement of the pulmonary venules and capillaries found in the lungs of all newborns dying of respiratory distress. As a result of uncompensated increased capillary hydrostatic pressure and increased capillary permeability, formed or nonformed elements to the blood may pass into the air spaces leading to pulmonary lesions of hemorrhage, hyaline-like membranes or edema. Hyaline-like membranes, although contributing to hypoventilation, are merely a pathologic result in the same category as pulmonary lesions of hemorrhage.

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Fever Curve as an Indicator for Steroid Therapy in Miliary Tuberculosis*,**

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A report rendered a short time ago by an outstanding committee of chest physicians concluded: "Apart from meningitis, there are no clearly formulated indications for adjunctive hormone therapy in tuberculosis."[1]

Within the past few years, steroid therapy in tuberculosis has been explored in special individual cases[2-4] and in controlled studies.[5-7] The use of ACTH and cortisone or its derivatives has been extolled in hypersensitivity states,[8] acute caseous and far-advanced pulmonary tuberculosis,[4,6,9-11] miliary[12-14] and meningeal tuberculosis[15-17] and tuberculous pleurisy.[18,19]

The majority of clinical surveys illustrate the value of steroids used in conjunction with antituberculosis chemotherapy as measured by patient survival, clinical and radiographic improvement, cavity closure, and shortened hospital stay.

It is still apparent, however, that clear-cut indications for steroids in tuberculous infections remain to be defined clearly and certainly long term follow-up of these patients must be evaluated critically.

Results

A clinical review of 26 adult cases of uncomplicated miliary tuberculosis proved most rewarding when it was observed that the fever curve in 75 per cent was most typical and quite frequently became a valuable aid in establishing a working diagnosis of disseminated tuberculosis.

During the first two weeks of hospitalization, temperatures ranged from 103° to 105°F. and the third to fifth weeks were marked by daily spikes from 101° to 103°F. In the sixth and seventh weeks, elevations were noted from 100° to 102°F. and from the seventh to thirteenth week, a low-grade temperature of 99° to 100°F. was frequently encountered.

It is of particular interest to point out that the curve was not appreciably altered by triple drug therapy, that is, isoniazid, streptomycin, and para-aminosalicylic acid.

TABLE 1—TYPICAL FEVER CURVES OF PATIENTS WITH MILIARY TUBERCULOSIS WHILE ON ANTITUBERCULOSIS CHEMOTHERAPY

Case No.	Week No. 1	2	3	4	5	6	7-13
4	106.4	105.6	103.2	102.8	100.8	100.6	98.6
7	103.8	103	102.8	102	102	102	101-98.6
9	104.8	104	102.4	102.4	102.4	102	100.4
13	105	104	103.4	102	101.2	101.2	99

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**Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, June 8-12, 1960.
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The typical fever curves of several representative cases are illustrated in Table 1. During weeks one and two, note 103° to 106.4°F. temperature spikes. In the third and fourth weeks, 102° and 103°F. are consistently indicated, with a gradual decline from the fifth to thirteenth week.

The fever curves of all patients are summarized in Figure 1 where we note a straight line descent in temperature over a 13-week period.

The average patient became afebrile by the ninth week. Table 2 indicates that three cases became afebrile between the third and sixth weeks and eight in each of the next two periods, that is, the seventh to tenth week and the eleventh to sixteenth week. Biehl,[20] in a series of 68 patients with miliary disease, also noted "that it often took ten weeks before fever returned to normal," although his average was somewhat lower than the present group. In Clark's[21] (*et al.*) series using isoniazid alone in the treatment of miliary tuberculosis, completely normal temperatures were attained between the fifth and seventh weeks. An analysis of the five deaths in this series revealed a secondary temperature rise in four instances. The fifth patient could not be evaluated as death occurred on the sixth hospital day. Table 3 represents the weekly temperature peaks of a 20 year-old woman admitted to the hospital with a three month history of weight loss and one month of fever, cough, and night sweats. Her past and family history were non-contributory. Physical examination

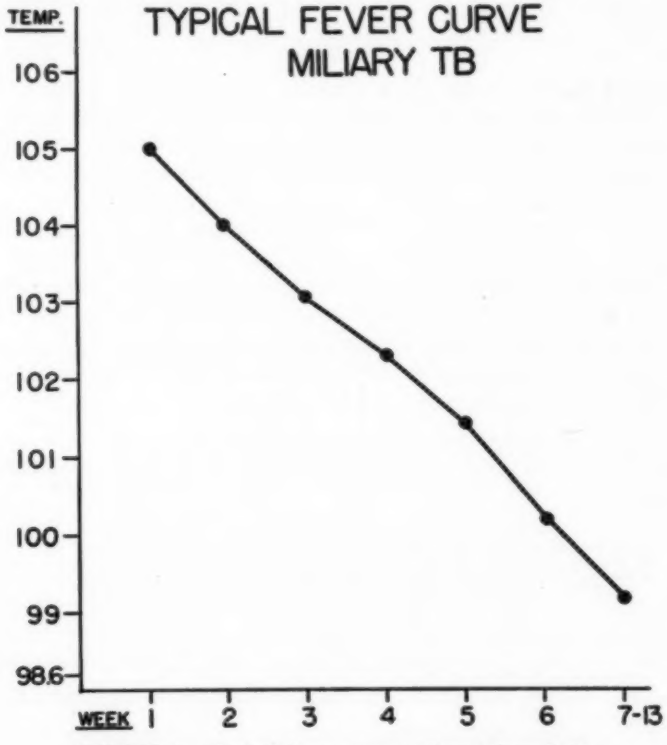

FIGURE 1: Typical fever curve, miliary tuberculosis.

TABLE 2—PATIENTS COMPLETELY AFEBRILE

3 - 6 weeks	3
7 - 10 weeks	8
11 - 16 weeks	8

revealed diffuse inspiratory crepitant rales in both lung fields and enlarged liver. Chest x-ray film revealed a miliary process and sputum cultures were positive for acid-fast bacilli. On admission, daily streptomycin, isoniazid, and PAS were initiated. The temperature elevations (Table 3) in weeks one, two and three, with a gradual decline toward a more normal temperature can be observed. Between the third and fourth weeks there was a break in the curve with spikes to 104° and 105°F. Death due to disseminated tuberculosis took place during the seventh hospital week. Figure 2 demonstrates in graphic form the initial curve, the secondary rise, and subsequent course.

The other deaths exhibiting a similar pattern were due to the overwhelming miliary process or complicating tuberculous meningitis.

Steroid therapy, cortisone initially and prednisolone more recently, was life saving in five cases where it was immediately prescribed for patients noted to have a secondary rise in temperature. This usually occurred between the third and fourth weeks of conventional drug ther-

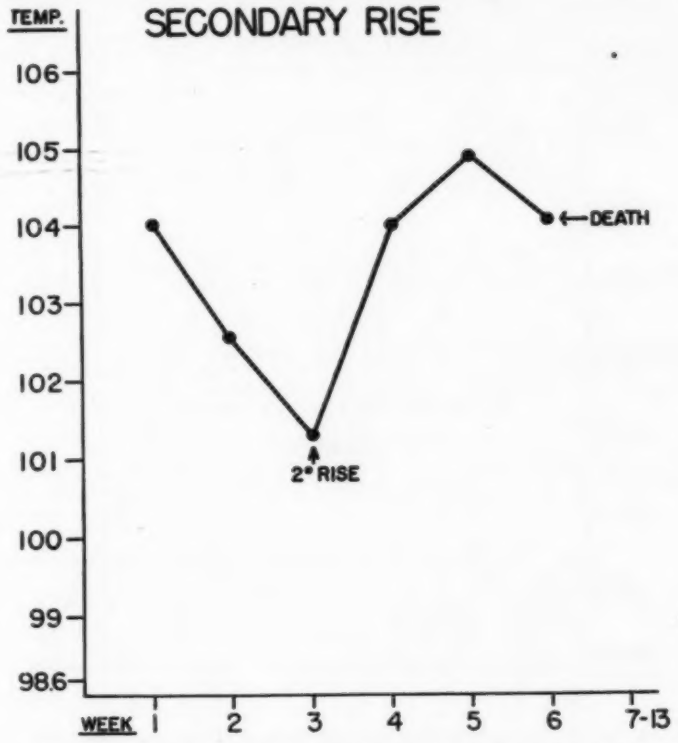

FIGURE 2: Fever curve indicating secondary temperature rise.

TABLE 3—FEVER CURVE OF PATIENT WHO DIED DURING THE SEVENTH WEEK OF ANTITUBERCULOSIS CHEMOTHERAPY

Case No.	Week No. 1	2	3	4	5	6	7
1	104°F.	102	101	104	105	103.6	death

apy. While a temperature elevation may be the only manifestation of a drug reaction, there was no indication of such an occurrence in any of the above patients. Our experience in the previously presented fatal cases taught us that the secondary temperature spike was most likely due to further spread of the disease or an impending fatal complication.

Table 4 notes the febrile course of a 43 year-old woman admitted with a month's history of fever, night sweats, and weakness. Her husband had tuberculosis. She had wheezing in both lung fields and a palpable liver edge. Chest x-ray film revealed miliary shadows and sputum smears initially and subsequent cultures were positive for acid-fast bacilli. Streptomycin, PAS, and isoniazid therapy was instituted shortly after hospitalization. After an initial clinical response, her condition took a turn for the worse with marked deterioration and secondary temperature rise during the fourth week (Table 4). Cortisone at this point resulted in an alteration of the fever curve toward a more normal pattern and her

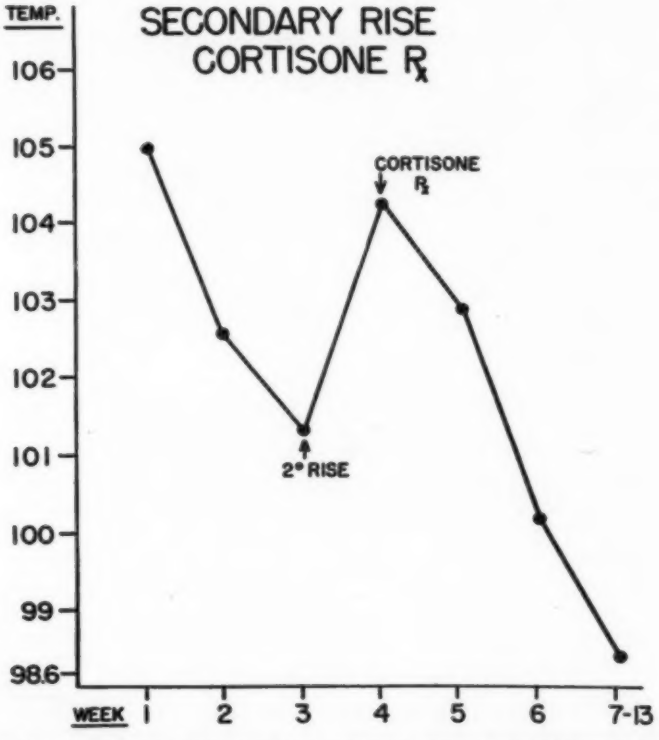

FIGURE 3: Fever curve, secondary rise, cortisone therapy and subsequent improvement.

TABLE 4—FEVER CURVE OF PATIENT STARTED ON CORTISONE AFTER SECONDARY TEMPERATURE RISE AT FOURTH WEEK

Case No. 14	Week No. 1	2	3	4	5	6	7-13	afebrile week 16
	105	102	101	104 (cortisone)	102.6	100.2	101-99	Degrees F.

subsequent improvement. Figure 3 illustrates in graphic form the temperature curve, secondary rise, cortisone administration, and hospital course.

Comment

The complications of hormone therapy are well known. Howell and Ragan[22] have recorded 41 different untoward effects. Many were of minor clinical importance, but those of peptic ulceration (some with bleeding or perforation), psychiatric disturbances, diabetes, hypertension, edema, superimposed bacterial infections, and electrolyte problems are most disturbing. This is of greater clinical concern at the present time since many of the patients we are admitting with miliary disease are 50 years or older.

Des Autels and Pfuetze[23] reported a survival rate of 33 per cent in patients treated with streptomycin alone or streptomycin-promin combination for miliary disease and an 83.3 per cent survival in patients treated with streptomycin and PAS. A survey of another general hospital in this country[20] revealed a survival rate of 77 per cent in uncomplicated cases of miliary tuberculosis who had received more than seven days of chemotherapy.

Clark *et al.*[21] observed no death in the cases treated with isoniazid and in 1957, the Veterans Administration-Armed Services Cooperative Study[24] noted that the estimated survival rate at two years after the start of isoniazid-streptomycin therapy was 95 per cent.

We have treated the last ten patients, several of whom are not included in the present analysis, without fatality. Seven patients received standard triple therapy and three, additional prednisolone. Our steroid schedule ranged from 20 to 40 mg. prednisolone for one to two weeks with a gradual decreasing dosage regimen for an additional four to eight weeks period.

SUMMARY

The diagnostic value of the fever curve in miliary tuberculosis is illustrated; the significance of the secondary temperature rise has been demonstrated and should be utilized as a specific indicator for steroid therapy in miliary tuberculosis.

RESUMEN

El valor de la curva térmica en la tuberculosis miliar se demuestra; la significación de la elevación secundaria de la temperatura se señala y debe utilizarse como un índice específico para el uso en el tratamiento de la tuberculosis miliar con esteroides.

RESUMÉ

L'auteur illustre la valeur diagnostique de la courbe thermique dans la tuberculose miliaire. Il démontre la signification de la poussée secondaire de température et il pense qu'elle devrait être considérée comme une indication spécifique de la thérapeutique par les cortico-stéroïdes dans la tuberculose miliaire.

ZUSAMMENFASSUNG

Die diagnostische Bedeutung der Fieberkurve bei der Miliartuberkulose wird erläutert; die Bedeutung des sekundären Temperaturanstieges wurde demonstriert und sollte als eine spezielle Indikation für die Steroid-Therapie bei der Miliartuberkulose dienen.

Complete reference list will be published in the reprints.

The Significance of Bronchiectasis Complicating Lung Cancer

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Bronchiectasis is no longer a major surgical problem. It is still a technical problem, with segmental resection of the lung, lobectomy, and pneumonectomy demanding a highly developed surgical skill. Every year the number of cases of bronchiectasis requiring surgical help is decreasing; quite the contrary is the steadily growing number of lung cancers operated upon.

The reason for this is that physicians nowadays know very well how to treat the infection of the bronchial tree and pneumonias in childhood, which often caused bronchiectasis. Besides, tuberculosis is decreasing in our civilized countries. Tuberculosis of the hilar lymph nodes, formerly an important cause of bronchiectasis in childhood, seldom is seen. Therefore, recurrent lung infections, as well as healed tuberculosis, formerly the main reason for resection therapy in cases of bronchiectasis, now scarcely are seen.

Only those patients who develop bronchiectasis distal to a bronchostenosis of any kind (a foreign body, a benign or malignant tumor) still require surgical help. The stagnation of mucus behind the stenosis always will favor the occurrence of renewed inflammations in the occluded area once infection has occurred. No treatment with antibiotics can give a definite cure. If we cannot remove the cause of the bronchostenosis by bronchoscopic treatment, resection is needed.

From 1947 through 1960, we saw in our surgical department 184 cases of bronchiectasis against 1357 cases of lung cancer in the same period. The number of cases of bronchiectasis requiring operation decreased greatly in the last years.

The etiology of these 184 cases of bronchiectasis was as follows:

1. Chronic pneumonia with recurrent lung infections	144 cases (77 male, 67 female)
2. Tuberculosis (cured as such)	29 cases (21 male, 8 female)
3. Foreign bodies	4 cases
4. Recurrent hemoptysis (congenital bronchiectasis)	3 cases
5. Besnier-Boeck, carcinoid, pneumoconiosis, bronchial adenoma	4 cases

Of these 184 patients, surgical treatment was performed in 173 cases (99 male, 74 female):

Segmental resection	15 cases
Lobectomy	126 cases
Pneumonectomy	24 cases
Pleuropneumonectomy	4 cases
Thoracoplasty	4 cases

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So, like Husfeldt, we think segmental resection has a very limited place in the treatment of bronchiectasis.

As may be expected, the operation is followed by some complications in a large percentage of cases, most of them caused by the fact that infected tissue must be removed.

POSTOPERATIVE COMPLICATIONS IN OUR 173 RESECTIONS		
None	102	
Infection of lung or pleura	19	
Lung embolism	7	(one died; one patient is completely cured after removal of a large embolus from the contralateral pulmonary artery on the ninth day). Fig. 1.
Other complications	38	
Died	7	(4 per cent)

It may be expected that the presence of bronchiectasis caused by bronchial obstruction in cases of bronchial cancer is playing some role in the treatment of lung cancer. Husfeldt is right in saying that the symptoms of the tumor as such cover, in a large part, the symptoms caused by the complicating bronchiectasis, but in our opinion these symptoms are by no means to be neglected; they must be separated from the symptoms caused by the tumor itself. Many patients are not sent to the surgeon because of the severe symptoms which even make an operation apparently hopeless. However, these symptoms and this bad condition, often ascribed to an extensive tumor, even having spread, are in fact often not caused by the tumor, but by the infected bronchiectasis distal to the tumor and consequently, operation may very well be possible.

In our cases of lung cancer, the specimens showed distinct bronchiectasis distal to the tumor in 24 per cent. Of course, there is a much greater possibility of bronchiectasis when the tumor is situated nearer the hilum of the lung than when it is located more peripherally.

Localization	Bronchial cancer with bronchiectasis number	per cent		Bronchial cancer without bronchiectasis number	per cent	
Pulmonary bronchus	13	19	78%	9	6	29%
Lobar bronchus	41	59		36	23	
Segmental bronchus	7	10		38	24	
Round tumor (peripheral tumor)	7	10		73	47	
Unknown	2	2				
	70 cases			156 cases		

The presence of bronchiectasis distal to the tumor only influences the indication for operation when infection has occurred in the occluded areas, either a severe inflammation of the bronchial walls, or an infection of the pulmonary tissue around them.

It is exactly the presence of this infection that confuses the picture of symptoms or of the malignant tumor as such. The complicating infection never gives the patient a better chance of operation, but always makes the symptoms seem to be much worse, even so that an operation might seem to be quite hopeless.

The symptoms are both subjective and objective, acute and chronic.

The chronic symptoms are most frequent and are caused by low-grade infection distal to the tumor. The patient feels ill, tired, has some fever and shows emaciation.

The emaciation especially can give the patient such a bad appearance that a general spread of the tumor seems likely. In several of our patients, their physicians had denied the possibility of operation. Nevertheless, we could perform resection with good results in a large number.

In a smaller number of cases, the patient is acutely ill through the inflammation of the tissue distal to the tumor. In these cases, the patient may have high fever, feel very ill and not respond, only for a short time, to antibiotic treatment. The patient's course goes downhill quickly. Nevertheless, we performed pneumonectomy with good results; of course, in these cases there are more complications after the operation, such as bronchial fistula or empyema, as compared to non-infected cases. We had 70 cases of lung cancer with symptoms of infection before the operation, either caused by inflamed bronchiectasis only, or also by pneumonia in the occluded area. Bronchiectasis proved to be a much more frequent cause of the infection (fever and emaciation) than pneumonia (69 per cent and 8 per cent respectively). From these figures, the significance of infected bronchiectasis distal to the tumor proves to be important for the symptomatology. Something has to be said about pleural effusion in this connection. When it is found in cases of bronchial cancer it is generally considered a sign of the presence of an extensive tumor or even of spread in the pleura or thoracic wall. As this occasionally can be so in cases of pleurisy with great amounts of fluid recurring every time after removing it, this conclusion, in general, is not correct at all. This, we concluded in agreement with Graham and Goldman. In many of our cases, the inflammation of either the lung tissue or even more of the bronchiectasis distal to the tumor, proved to be the cause

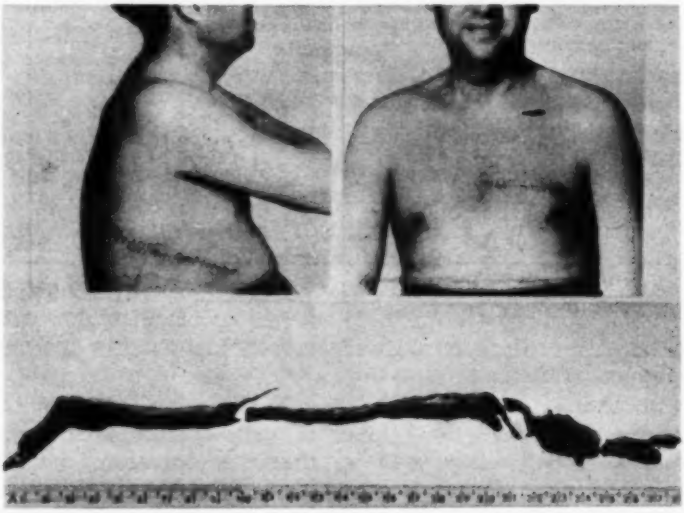

FIGURE 1: Massive pulmonary embolectomy on the ninth day after lobectomy for bronchiectasis.

of the pleurisy (up to one liter). This was so in most cases of serous fluid, but even at times of hemorrhagic fluid. Therefore, we did not consider the presence of pleural effusion as such a contraindication against operation. Of course, after opening the thorax, we found several cases inoperable, either because of local extension of the tumor, or because of the presence of carcinosis of the pleura. Nearly half of our cases were, quite to our surprise, resectable. No sign of carcinosis pleurae was seen in these resected cases.

RESECTABILITY IN 38 PATIENTS WITH LUNG CANCER AND PLEURAL EFFUSION

	Number of Cases	Serous Fluid	Hemorrhagic Fluid
Non resectable	21	11	10
Resectable	17	15	2

Thus, even the presence of hemorrhagic effusion is not an absolute contraindication against thoracotomy, as resection may very well be practicable.

In patients with bronchial cancer with (mostly infected) bronchiectasis, we found more postoperative complications, such as empyema, bronchial fistula, wound infection, as in patients with bronchial cancer without bronchiectasis. The differences, however, were only slight: 8.6 per cent and 5.1 per cent respectively. When we compared the frequency of all kinds of postoperative complications in both groups of patients, no difference could be found.

POSTOPERATIVE COMPLICATIONS AFTER 226 PULMONARY RESECTIONS FOR CANCER

	Patients with lung cancer and bronchiectasis			Patients with lung cancer without bronchiectasis		
Total number of cases	70			156		
Complications:	Number	Per cent		Number	Per cent	
Emphyema	3	4.3	8.6%	6	3.8	5.1%
Lethal pneumonia	—			2	1.3	
Bronchial fistula	1	1.4		—		
Wound infection	2	2.9		—		
Thrombosis	1	1.4		4	2.5	
Pulmonary embolus	—			9	5.8	
Fibrillation of the heart	4	5.7		7	4.5	
Heart death	1	1.4		—		
Atelectasis	1	1.4		3	1.9	
Hemothorax	—			1	0.7	
Gastric hemorrhage	1	1.4		—		
Total		19.9			20.5	

From a technical point of view, there is no contraindication to be found either in the presence of infected bronchiectasis in lung tissue distal to the tumor, or in the presence of intrapleural fluid. Only the establishment of an extension of the tumor in the thoracic wall, or deeply in the mediastinum as seen by bronchoscopy and bronchography, or the establishment of spread outside of the lungs, in lymphatic nodules in the neck or elsewhere in the body, or in the pleura as proved by finding malignant cells in the pleural effusion, form a contraindication to

operation. If emphysema does not prevent surgical therapy, this should be done in all other cases.

It might be, however, that the resection of pulmonary cancer in the presence of pleural effusion would not be followed by a reasonable percentage of five year cures. In other words, pleural effusion still means a tumorous spread, even when not found at operation.

We reviewed our 547 cases, who were operated upon before 1954, so that the percentage of five year survivals could be studied.

PATIENTS WITH LUNG CANCER FROM 1946-1954

Bronchial carcinoma	547 cases
Resection performed (lobectomy or pneumonectomy)	137 cases (25 per cent)
Of these 137 resected cases, 37 patients were living and well after five years (27 per cent)	
On 17 patients, resection was performed in the presence of pleural effusion; four were alive and well after five years (23 per cent)	
On 47 patients, resection was performed in the presence of bronchiectasis; ten patients were alive and well after five years (21 per cent)	

From these figures it follows that neither the presence of bronchiectasis distal to the tumor (infected or not) nor the presence of pleural effusion gives a bad prognosis, when resection can be performed.

Discussion

From a technical point of view the resectability in patients with lung cancer is hardly influenced by the pre-operative establishment of bronchiectasis, infected or not, nor does the presence of pleural effusion do so.

Neither bronchiectasis nor pleural effusion influences to any important extent the postoperative course or the percentage of five year survivals.

Generally, when not clearly understood, the symptoms of infection distal to the tumor or the presence of pleural effusion, cause various physicians to advise against operation, these symptoms being ascribed to general spread. However, we found perfect resectability in a very high percentage of cases and even a reasonable percentage of five year cures.

SUMMARY

The number of cases of common bronchiectasis needing surgical treatment is decreasing greatly nowadays. Infected bronchiectasis distal to a malignant bronchial tumor may cause severe symptoms to the patient, but as such, does not constitute a contraindication to thoracotomy. Neither is the presence of pleural effusion, as found before the operation a contraindication, resection being possible in nearly half of the cases with good results.

The only reason not to operate on a patient with lung cancer is proved inoperability for technical reasons or proved spread outside the lung. Fever, impression of illness or bad general condition is by no means in most cases caused by the tumor itself, but more often by the infection distal to the tumor and that is no reason to refuse operation.

RESUMEN

El número de casos de bronquiectasia común que necesita tratamiento quirúrgico, está ahora decreciendo grandemente. La bronquiectasia detrás de un tumor maligno puede causar graves síntomas al enfermo, pero como tales no constituyen una contraindicación a la toracotomía.

Tampoco lo es el encontrar líquido intrapleural antes de la intervención siendo la resección posible en cerca de la mitad de los casos con buenos resultados. La única razón para no operar un enfermo con cáncer del pulmón, es la inoperabilidad demostrada por razones técnicas a la diseminación demostrada fuera del pulmón. La fiebre, la impresión de mal aspecto o mal estado general no son causados de ninguna manera por el tumor mismo sino mas a menudo por infección detrás de el y no hay razón para rehusar la operación.

RESUMÉ

Le nombre des cas de bronchectasie commune nécessitant un traitement chirurgical est maintenant en nette décroissance. Une bronchectasie infectée sur une tumeur bronchique maligne peut provoquer des symptômes graves chez le malade, mais comme telle, ne constitue pas une contre-indication à la thoracotomie. De même la présence de liquide intrapleural, trouvé avant l'opération, n'est pas une contre-indication à celle-ci, la résection étant possible dans près de la moitié des cas avec de bons résultats.

La seule raison de no pas opérer un malade atteint de cancer pulmonaire est la mise en évidence de son caractère inopérable pour des raisons techniques, ou d'une dissémination extrapulmonaire. La fièvre, l'impression de souffrance ou un mauvais état général ne sont en aucune façon dans la majorité des cas provoqués par la tumeur elle-même, mais plus souvent par l'infection surajoutée, et ce n'est pas une raison pour refuser l'opération.

ZUSAMMENFASSUNG

Die Zahl der Fälle mit gewöhnlichen Bronchiektasen, die einer chirurgischen Behandlung bedürfen, wird jetzt beträchtlich geringer. Infizierte Bronchiektasen distal von einem malignen Bronchialtumor können für den Patienten schwere Symptome bewirken, stellen aber als solche keine Kontraindikation zur Thorakotomie dar. Ebensowenig ist das Vorhandensein eines intrapleuralen Ergußes, wie man ihn vor der Operation findet, eine Kontraindikation und eine Resektion in fast der Hälfte der Fälle mit guten Ergebnissen möglich.

Der einzige Grund, einen Fall von Lungenkrebs nicht operativ anzugehen, ist seine nachgewiesene Inoperabilität aus technischen Gründen oder die nachgewiesene Aussaat außerhalb der Lungen. Fieber und ein schlechter Gesamteindruck oder übler Allgemeinzustand werden keineswegs in den meisten Fällen durch den Tumor selbst hervorgerufen, sondern weit häufiger durch die Infektion distal vom Tumor, und dies ist kein Grund die Operation abzulehnen.

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FUNCTIONAL CHANGES OF THE THYROID GLAND IN ATHEROSCLEROSIS

The influence of ascorbic acid and iodine on the functional activity of the thyroid gland was assessed in patients afflicted with atherosclerosis. Under the effect of ascorbic acid there was seen a distinct rise of radioiodine absorption by the thyroid gland. In the control group of healthy subjects, the increase of absorption was not as marked. In atherosclerosis, patients and healthy subjects, the basal metabolism manifested no essential changes.

Vainbaum, Y. S.: "Functional Changes of the Thyroid Gland in Atherosclerosis, Patients under the Influence of Ascorbic Acid and Iodine," *Clinical Medicine (USSR)*, 39:108, 1961.

Pleural Biopsy and Thoracentesis by a New Instrument*

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Since DeFrancis *et al.*[1] first described needle biopsy of the parietal pleura in 1955, this aid to diagnosis of causes of pleural effusion has received much interest. According to previous reports, needle biopsy has been diagnostic in about one-half of the cases in which it has been used. However, it should be realized that some of these cases were selected and that needle biopsy of the parietal pleura may not be this efficacious if used in *all* cases. If the diagnosis appears obvious on the basis of other clinical evidence, then pleural biopsy is not recommended. If there is some question as to the cause of the pleural effusion, then Donohoe's[2] approach is advisable: "At the time of the initial thoracentesis, aspiration biopsy should be performed. If a specific cause is determined, no further diagnostic studies would be needed and appropriate treatment may be instituted. If such a specimen is either inadequate or inconclusive, either a repeat aspiration biopsy is in order or surgical biopsy through a small intercostal approach should be undertaken. A frozen section should be obtained and if a specific cause is demonstrable, the incision may be closed. If the result is not diagnostic, then the surgeon should extend the incision and full exploration with appropriate biopsy and/or resection can be carried out, followed subsequently with appropriate treatment."

The Vim-Silverman needle has generally been used as originally described by DeFrancis.[1] Following this procedure, thoracentesis must be done next. Either procedure, particularly the latter, may be complicated by pneumothorax due to puncturing or lacerating the lung. In order to combine pleural biopsy and thoracentesis and also to lessen the risk of pneumothorax, we have devised a new instrument. It has features somewhat similar to those previously described by Cope,[3] but it is more similar to that reported by Abrams.[4] The purpose of this article is to describe this instrument and its use, report our results in using it and compare the apparent efficacy of this instrument to others. We are not attempting to prove the merits of pleural needle biopsy, for we feel this has been done.

Description of Instrument

The instrument consists of two parts—the "sheath" and the "needle" and is shown in Fig. 1. The outer "sheath," A, has a hook-like cutting notch on one end and a collar with three grooves on the other end. The needle, B, has a boss protruding from its hub which fits in the grooves of the collar of the sheath. The sheath has a diameter of a size 13 needle and the needle, B, fits within this snugly enough to be airtight.

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After adequate anesthetization of the chest wall, a 4 or 5 mm. superficial incision is made in the skin to allow easy introduction of the instrument. A syringe (and intervening three-way stop cock, if desired) is fitted into the hub and the needle is inserted into the sheath. The boss is slipped into the deepest groove of the collar and rotated so as to "lock." This allows the point of the needle to extend beyond the sheath, as in C. The instrument is then inserted in the manner customary in performing thoracentesis. When fluid is aspirated into the syringe, the needle, only, is withdrawn, slightly, and rotated so that the boss is locked in the second groove and then the point of the needle no longer extends past the end of the sheath—as shown in D. In this position fluid may be aspirated without danger of puncturing the expanding lung and causing pneumothorax.

To biopsy the parietal pleura the boss is unlocked and the needle pulled back only far enough within the sheath so that the cutting notch is fully opened. Slight lateral pressure of the entire instrument in the direction of the cutting notch (indicated by an arrow engraved in the collar) is made and it is withdrawn until resistance is met due to the hook-like edge of the cutting notch engaging the parietal pleura. With the sheath portion of the instrument being held carefully in place the needle is again rotated so that the boss engages in the third groove, shown in E. As the needle is then slipped forward that portion of the parietal pleura which has been caught within the cutting notch will be sheared off, as shown in F. The instrument is then withdrawn and the biopsied pleura will be found within the distal end of the sheath from which it may be obtained by pushing a small wire through from the other end.

Present Study

In the present study, 47 patients with pleural effusion of previously undiagnosed cause had thoracentesis and pleural biopsy with the above-described instrument. In this study, the cases were unselected in that we

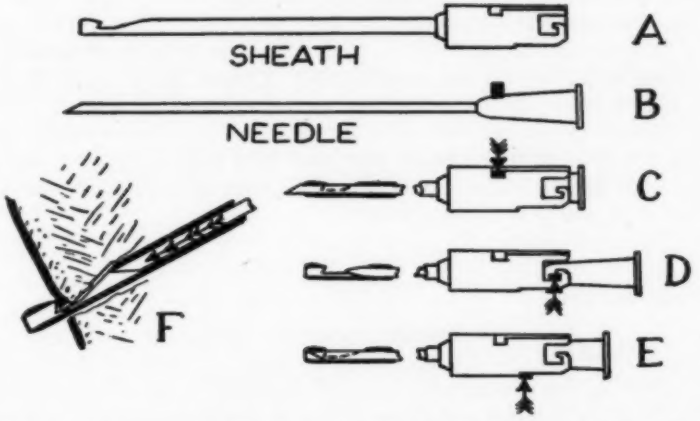

FIGURE 1: Instrument described in present report. Single arrows indicate positions of needle boss in various grooves of the collar of the sheath. Double arrow indicates how point of needle is pushed forward to biopsy the parietal pleura.

did not exclude cases because the underlying condition appeared to be one which might not be diagnosable by pleural biopsy. In the majority of cases, two pleural specimens were obtained at one sitting and when this was done the two were processed together and considered as one for purposes of tabulation. Two of the patients had biopsies at two different times. The "final diagnoses" were those made at times of discharge of the patient or after follow-up in the outpatient clinics. Diagnosis was confirmed by necropsy in nine cases and thoracotomy in seven cases. The "biopsy diagnoses" used were the original pathologist's reports placed in the chart, except one which was originally reported as negative but when later reviewed showed very obvious malignancy. A specimen was considered adequate if the biopsy contained sufficient material for a diagnosis of malignancy, granuloma or inflammatory reaction or if it showed mesothelial cells.

Results

The histologic diagnoses related to the final diagnoses in this series is indicated in Table 1. In this study, only cases of carcinoma were diagnosed by pleural biopsy. Thirteen of all 47 cases (28 per cent) or 59 per cent of the 22 carcinoma cases were thus diagnosed. The one granuloma found was from a patient with a subphrenic abscess and did not aid in the diagnosis in that case. In 26 cases, nonspecific pleuritis was found. Although this histologic picture is not absolutely diagnostic, it is often helpful clinically and in most of these instances is fully compatible with the final diagnosis.

The finding of normal pleura in three of the cases is not surprising in that in cases of carcinoma, the pleura is frequently found to be normal except in areas of invasion or metastatic implantation. Also, there may be no significant pleural reaction in cases of congestive heart failure, in that the pleural fluid in these cases may be only an increased amount of the normal pleural fluid which is a transudate.

Four of the 47 specimens (8.5 per cent) failed to show evidence of parietal pleura. Such specimens showed only connective tissue and muscle. However, one may speculate that pleura may have been obtained on the biopsy but because of its thin structure may be missed by the microtome if not in the plane of section. This is, no doubt, a situation which might take place in needle biopsy of the pleura with any instrument. Table 2 shows how our results compare with other workers' series.

Incidentally, this instrument was also used successfully in one pericardial, one synovial, and one of two peritoneal biopsies. Carcinoma was diagnosed in the pericardial biopsy.

TABLE 1—RESULTS OF PRESENT STUDY

Final Diagnosis	Histologic Diagnosis				
	Malignancy	Granuloma	Normal Pleura	Nonspecific Pleuritis	Inadequate Specimen
Carcinoma	13	0	1	5	3
Tuberculosis	0	0	0	5	0
Nontuberculous infection	0	1	0	9	0
Congestive heart failure	0	0	2	2	1
Miscellaneous	0	0	0	5	0
	13	1	3	26	4

TABLE 2—NEEDLE PLEURAL BIOPSY RESULTS

Author	Instrument	Number Patients	Number Biopsies	Cases Diagnosed All Cases No.	All Cases per cent	Carcinomas No.	Carcinomas per cent	Insufficient Specimen
Heller *et al.*[5]	V-S*	45	79	14	31***	8	50***	3
Mestitz *et al.*[6]	A**	116		72	62	7	25	9
Welsh[8]	V-S	17		10	59	10	72	
Samuels *et al.*[9]	V-S	52		25	48	21	55	
Donohoe *et al.*[10]	V-S		78	30	38	8	42	18
Harvey *et al.*[11]			42	14	33			
Weiss[12]		31	31+	23	74			
Sweany[13]	V-S	88	106	23	26	10	50	
	V-S 9 cases	20	22					
Leggat[7]	A 20 cases			12	60	12	60	1
Present Study		47	49	13	28	13	59	4

*V-S=Vim-Silverman Needle

**A=Abram's Needle

***Number of patients used as denominator when stated. Otherwise number of biopsies used as denominator.

Discussion

This instrument seems to have satisfactorily fulfilled its purpose in simultaneous performance of thoracentesis and pleural biopsy. The only complication sustained was pneumothorax and subcutaneous emphysema in one patient. However, it must be pointed out that free pleural fluid was *not* present in this case and we now agree with Heller *et al.*[5] that the lung must be clear of the chest wall as a definite prerequisite to pleural biopsy. That this instrument is not difficult to use is illustrated by the fact that in the collection of the present series many house staff physicians used it for the first time without difficulty.

Table 2 shows the results obtained by performers of nonsurgical pleural biopsy. For the most part, they have used the Vim-Silverman needle, except Mestitz *et al.*,[6] who used Abrams'[14] needle in all cases and Leggat[7] used both types but found the latter to be preferred. It is not possible to compare accurately the efficacy of methods in two series of cases since the etiologies of the effusions may be quite different. From studying the literature, it becomes obvious that cases of pleural effusion due to carcinomas are most readily diagnosed by this means, as is shown in Table 2. Therefore, to evaluate the efficacy of this instrument, we should confine the comparison to the percentage of cases of carcinomatous pleural effusions diagnosed.

It is unlikely that any instrument can improve upon the diagnostic efficacy of pleural biopsy as shown in Table 2. Even though the parietal pleura might be thickly studded with malignant implants or other lesions, a diagnosis cannot be made unless the few square millimeters of pleura obtained is involved. Whether or not diagnostic material is obtained is largely a matter of chance. At any rate, the *statistical* chance of making the diagnosis by biopsy at the time of thoracentesis is so good, and the risk of complications so slight, that we believe it should be done in every case where the diagnosis is even remotely in doubt.

SUMMARY

A new instrument for simultaneous performance of thoracentesis and pleural biopsy is described. This instrument is considered safer than previous thoracentesis or biopsy needles in that, after initially entering the pleural space, a sharp point does not project towards the lung.

Twenty-eight per cent of all 47 cases, or 59 per cent of 22 *carcinoma* cases on which this instrument has been used, were diagnosed by the pleural biopsy. Only four biopsies failed to yield a satisfactory specimen.

RESUMEN

Se describe un instrumento nuevo para llevar a cabo al mismo tiempo la toracentesis y labiopsia pleural. Este instrumento se considera mas seguro que las agujas de toracentesis o biopsia antes usadas porque después de haber entrado a la pleura no se proyecta una punta aguda dentro del espacio pleural hacia el pulmón.

En vientiocho por ciento de todos los 47 casos de carcionoma se usó este método.

En 59 por ciento o sean 22 enfermos de carcionoma en los que este instrumento se ha usado se hizo diagnóstico por la biopsia pleural.

Solo 4 biopsias dejaron de dar un espécimen satisfactorio.

RESUMÉ

L'auteur décrit un nouvel instrument pour la pratique simultanée de thoracentèse et de biopsie pleurale. Cet instrument est considéré comme donnant plus de sécurité que les aiguilles pour thoracentèse ou pour biopsie connues antérieurement, par le fait que, après la pénétration initiale dans l'esepace pleural, il n'y a pas de risque de projection d'une pointe aiguisée contre le poumon.

28% de 47 cas de différentes natures, ou 59% de 22 cas de cancers pour lesquels l'instrument a été utilisé furent diagnostiqués par biopsie pleurale. Il n'y eut que quatre biopsies qui ne fournirent pas d'échantillon satisfaisant.

ZUSAMMENFASSUNG

Es wird ein neues Instrument zur gleichzeitigen Vornahme einer Thorakocentese und pleuralem Biopsie beschrieben. Dieses Gerät wird für sicherer gehalten, als die bisherigen Nadeln zur Thorakocentese zur Biopsie in der Hinsicht, daß nach dem anfänflichen Durchtritt durch den Pleuralspalt keine scharfe Spitze gegen die Lunge gerichtet ist.

28% von allen 47 Fällen oder 59% der 22 Carzinome, bei denen dieses Instrument eingesetzt wurde, wurden mittels der pleuralen Biopsie diagnostiziert. Nur bei 4 Biopsien gelang es nicht, ein befriedigendes Präparat zu gewinnen.

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DIAPHRAGM GRAFTS

Animal experiments demonstrated extremely valuable qualities of the diaphragm for use in plastic surgery. Grafts of the diaphragm affixed to a pedicle and cut out with due consideration for their innervation and blood supply grow very well into the pericardium, cardiac muscle, aorta, lung, esophagus and liver. The clinical application of this method, begun in 1948, yielded good results in operations on the esophagus for tumors, cysts and diverticula. Here we noted the possibility of substituting the vascular wall of the esophagus with the diaphragmatic muscle. Good results were obtained in the application of diaphragmatic grafts affixed to a pedicle for closing the bronchial stump. In aneurysm of the heart, this method enabled us to improve the vascularization of the myocardium and to strengthen the scarred wall of the heart with diaphragmatic muscle. This method also is used in the following situations: closing defects of the wall or strengthening the line of anastomosis in operations on the esophagus; plastic operations on the cardia for cardiospasm; creating artificial cardiac sphincter in gastroesophageal regurgitation; and for closure of wounds of the lung, liver, heart and aorta incurred during operations on these organs.

Petrovsky, B. V.: "Use of Diaphragm Grafts for Plastic Operations in Thoracic Surgery," *J. Thor. and Cardio. Surg.*, 41:348, 1961.

Pulmonary Function Tests: Applications, Observations, Interpretations*

A Brief Summary of the Physiology of the Lung Together with a Discussion of the More Commonly Used Pulmonary Function Tests

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It is well recognized that pulmonary function tests have aided in the early recognition of pulmonary dysfunction in patients considered to be normal on the basis of clinical and radiological examination, and in the differential diagnosis of patients with a known pulmonary disease, but in whom a specific diagnosis could not be made with certainty by other methods.

The division of pulmonary function into the arbitrary categories of ventilation, distribution, and diffusion makes for easier discussion, but it should be noted that no single test is available at present which can be used to the exclusion of all others in the testing of these various categories. Different aspects of pulmonary function must be evaluated with different tests.

Ventilation

Ventilation may be defined as the process whereby air is moved into and out of the lungs. This aspect of pulmonary function, then, involves consideration of both the volumes of air moved, as well as of the factors inherent in moving the volumes of air, *i.e.*, the "mechanics" of breathing.

Ventilation and ventilatory impairment are usually evaluated with measurements of the conventional vital capacity, the timed vital capacity, and the maximal breathing capacity.[1] However, attention should first be directed to the concept of alveolar ventilation, since this is the volume of air which enters the alveoli with each inspiration and participates in active gas exchange. The amount of air moving into and out of the alveoli is obviously much more important than that moving in and out of the nose and throat.

Alveolar ventilation may be evaluated clinically by observation of the uniformity and adequacy of the chest cage expansion, the extent of the diaphragmatic excursions, and by auscultation of the breath sounds.[2] Such observations, however, are by no means quantitative insofar as volumes are concerned and may be misleading. Whenever there is any doubt as to the adequacy of alveolar ventilation, a quantitative determination should be done using the formula: Alveolar Ventilation=(Tidal vol. – Dead Space) x Frequency. The measurement of respiratory dead space is difficult, but in adults this can be considered to be approximately equal to the patient's estimated weight in pounds.[3]

Measurements of the vital capacity may be exceedingly difficult to evaluate, especially single measurements. A series of measurements, on

*Third Prize, 1959 Essay Contest, American College of Chest Physicians.

the other hand, is very helpful in demonstrating changes in an individual's pulmonary status. Determinations of vital capacity have been found to be most useful:[4]

1. when repeated observations are made on the same person,
2. when considered in relation to time, and
3. when used before and after bronchodilating agents.

The measurement of the vital capacity against time, the forced expirogram, is an excellent test, and is probably the most effective means at present of demonstrating an obstructive type of ventilatory abnormality.

Changes in the subdivisions of the vital capacity, the inspiratory capacity and the expiratory reserve volume are also difficult to evaluate in that rather marked variations may exist even in the same person.[5] However, considerable attention has been paid in the past to determinations of the residual volume of the lungs, that volume of air remaining after a forced expiration. This is one of the more important measurements used in quantitating the extent of pulmonary emphysema.

The maximal breathing capacity test has been used extensively as a means of expressing quantitatively the maximal rate at which the respiratory system can move volumes of air alternately into and out of the lungs. This test is essentially a test of total ventilatory function, since a satisfactory performance is dependent upon a proper functioning chest cage, a patent tracheobronchial airway, and normal elasticity of the lungs. Still, the very fact that it is "all inclusive" makes it of less value than it might be. Its applications and limitations have been much discussed.[6,7] The age for compulsory retirement would appear to have been reached for this old standby.

The Mechanics of Breathing

Consideration of the mechanical aspects of ventilation becomes important when one considers that even though lung volumes may be entirely within normal limits, the work, or expenditure of energy, required in the movement of air into and out of these "volumes" might be such that the patient is in all reality quite disabled. Recent studies stress the characteristics of air flow and of the physical properties of the lungs as indices of proper ventilatory mechanics.

Air flow in a system of tubes may be considered to be either laminar or turbulent. In smooth, straight tubes turbulent flow occurs only at high velocities, whereas in a many-branched tubular system, as is the tracheobronchial tree, eddy currents, or turbulent flow, is likely to be set up at the points of branching at lower flow rates. Also, eddy formation is particularly apt to occur at points of irregularity, such as might be caused by mucus, exudate, tumors, or foreign bodies in the airways. Turbulent flow is a less efficient type of air movement.

As air moves through the respiratory system, the result of a pressure gradient created by the "stretching" or increase in volume of the chest during inspiration, it necessarily overcomes certain resistive forces. These forces may be divided into:[8]

1. that force necessary to overcome the elastic resistance of the lungs and/or chest,

2. that force necessary to move nonelastic tissues, and
3. that force necessary to overcome resistance to airflow in the tracheobronchial tree.

Inertia in the system has been shown to be negligible.[9]

The force opposing the distortion of the lungs during an inspiration is the elastic force of the system. This force depends only upon the volume contained in the system at any given moment, and is studied at points of no air flow, since with air movement there are certain pressure differences caused by the pressure gradient required to move the air and the pressure required to deform the tissues. The important relation thus established, volume change per unit pressure change, when measured for the lungs alone, serves as an index of the "stiffness" of the lungs, a concept more properly termed the mechanical compliance of the lungs.[10]

The force necessary to move nonelastic tissues is that force required to overcome frictional resistance within the lung parenchyma and in the surrounding tissues which are deformed by the respiratory movements. The force necessary to overcome the resistance to airflow in the tracheobronchial system is a force of many variables, and is at present the most difficult of the forces to evaluate. Resistance in addition to that inherently present may be imposed by the use of certain external or artificial respiratory devices.

The work of breathing may be determined by the simultaneous measurement of the pressure gradient across the respiratory system and of the volume displacement of the system. If this is done, and the results plotted against each other for a complete breathing cycle, a loop is defined, the area of which equals the nonelastic mechanical work done by the system for that particular breath.[11] The elastic work done by the system during the same breath can also be determined from the same diagram. To the extent that the expiratory portion of the loop falls outside the elastic work area, active work is performed.

Distribution

The human lung is an organ with many septa, a condition which makes the uniform distribution of gas to the alveoli increasingly difficult. Indeed, in the healthy lung alveolar ventilation is not absolutely uniform. In the case of pulmonary disease, it may be decidedly uneven.[3]

Inspired air is distributed to the alveoli according to the influence of several factors, such as regional changes in the elasticity of the lung, the presence of airway obstruction, and regional changes in lung expansion.[12] These factors may act alone or in combination in the same or in different parts of the lung. While the physician is familiar with nonuniform ventilation in the form of regionally diminished breath sounds, it is important to remember that since alveolar ventilation is nonuniform even in healthy young individuals, a recorded abnormality by a relatively sensitive test is not necessarily an indication of disease. It is important to realize, too, that nonuniform ventilation can lead to pulmonary insufficiency even though the minute volume of breathing and the volume of the alveolar ventilation is normal.[3,4]

The present methods of measuring the distribution of air to the alveoli are deficient in that they do not take into account the work of breathing

or the evenness of distribution of the pulmonary capillary blood flow to the ventilated alveoli. The importance of these two parameters is such that distribution is probably better thought of as the ratio of alveolar ventilation to alveolar blood flow.[12]

Ventilation-Perfusion Relations

If a true picture of pulmonary function is to be obtained, it is essential that both the volume and distribution of the pulmonary capillary blood flow and the volume and distribution of the alveolar ventilation be known. The determining factor in the proper arterialization of the blood is the ratio of the alveolar ventilation to the pulmonary capillary blood flow, the so-called ventilation/perfusion ratio.[2,13] While absolute values for this ratio can be obtained, the important point is whether or not the same ratio exists for all parts of the lung. If it does, the blood will be arterialized maximally (for that particular volume of ventilation and blood flow), and if it does not, anoxemia may result. It has been postulated that "variations in ventilation/blood flow ratios . . . probably represent the most frequent cause of anoxemia in clinical medicine."[2] However, while variations in the ventilation/blood flow ratio do represent a source of alveolar-to-arterial pO_2 difference, it should be pointed out that this difference is actually the immediate effect of a variation in either or both members of the ratio, and not the end result of such a variation. There is no actual difference between the pO_2 of alveolar gas and that of end-pulmonary capillary blood as there is in the case of an anatomical shunt, or in impairments of diffusion. Alveolar-to-arterial pCO_2 differences, which also occur on the basis of variations in the ventilation/blood flow ratio, are necessarily less than the corresponding pO_2 difference because of the peculiar characteristics of the CO_2 dissociation curve.

Diffusion

If the mixed venous blood coming to the alveoli is to be properly arterialized, other things being equal, there must be no impediment to the diffusion of the respiratory gases across the alveolar-capillary membrane. The facility with which such diffusion takes place can be evaluated by two rather different approaches: by study of the blood gases, and by determination of the "diffusing capacity of the lung."

Blood gas studies: Examination of blood samples for the purpose of assaying pulmonary function must be done on arterial blood because of the unpredictable variations of the oxygen and carbon dioxide concentrations of venous blood, regardless of the part from whence it comes.[14]

In regards to oxygen, blood is examined primarily either for the per cent saturation of the hemoglobin, or for the oxygen tension. Accurate chemical and photometric methods of analysis should replace for the physician his visual impressions of blueness, since these are not reliable and, indeed, may be quite misleading.[2]

The lower limits of arterial O_2 saturation compatible with a moderately active existence are not known. Neither is there information on the variability of O_2 saturation from hour to hour, or from day to day in healthy subjects. Hypoxemia need not be present even with serious pulmonary disease, nor is the O_2 saturation necessarily lowered after pneumonect-

omy if the remaining lung is healthy. Therefore, isolated determinations of arterial O_2 saturation must be interpreted cautiously. The measurement of the O_2 tension is a more sensitive index of altered pulmonary physiology, especially when the O_2 saturation is nearly normal.[4] It will be recalled from the shape of the dissociation curve for oxyhemoglobin that rather marked reductions in pO_2 may occur before these reductions are reflected in the values for O_2 saturation.

The interpretation of values obtained for carbon dioxide may be more difficult in that CO_2 may exist in the blood in several ways: as CO_2 in solution, as carbonic acid, as CO_2 in combination with plasma proteins and with hemoglobin, and as bicarbonate. Bicarbonate, in both the red cells and plasma, accounts for the major portion of all the CO_2 present.[15] Under normal circumstances, the CO_2 tension in the alveolar gas mixture is held relatively constant at about 40 mm.Hg. The high diffusivity of CO_2 (about 25 times that of oxygen) means that the CO_2 tension of the blood leaving the lungs is the same, for all practical purposes, as that in the alveolar air. This remains true even through alveolar-capillary diffusion is severely impaired, and it is in this close relation that lies the value of peripheral arterial blood CO_2 determinations.

Therefore, it may be reasoned that an increase in arterial pCO_2 must mean that the whole lung, or a major portion of it, is underventilated. Conversely, decreases in arterial pCO_2 must mean that the whole lung, or a major portion of it, is overventilated. Caution must be exercised here, however, since such may be the result of venous-to-arterial shunts, diffusion difficulties, or of uneven ventilation/blood flow ratios. A low pCO_2 means only that there are alveoli remaining that are capable of being hyperventilated.[8]

Blood CO_2 values are also important in that determinations of this constituent are often resorted to in attempts to resolve certain problems of acid-base balance. When used thus, it is important to remember that pH deviations may be either respiratory or metabolic in origin, and as a result, blood CO_2 values as generally determined, *i.e.*, CO_2 content, may be either high, normal, or low. For this reason, data on the CO_2 content of the blood should always be interpreted along with other ancillary data, or in conjunction with the patient's pulmonary status.

The diffusing capacity of the lung: The diffusing capacity of the lung is, by definition, the amount of gas transferred across the alveolar-capillary membrane per unit time for each mm.Hg. difference in partial pressure of the gas across the membrane. The diffusing capacity, then, is the result of several variables:[2] the surface area available for diffusion, the distance through which diffusion must occur, and the characteristics of the tissues through which the diffusion takes place.

The principle according to which the diffusing capacity is measured has as its basis the assumption that certain gases pass through the alveolar capillary membrane solely by diffusion, and that these gases are more soluble in blood than in the membrane.[16] There are at present only two such gases that qualify, oxygen and carbon monoxide. Each owes its qualifications to its peculiar reactions with hemoglobin. Both presumably measure the same thing.

There is a certain amount of reserve associated with the diffusing capacity. With increasing work loads, there is an increase in the diffusing capacity up to a limit which is approximately 3 to 4 times the resting diffusing capacity.[17] The change from a moderate to the maximal diffusing capacity occurs suddenly, an event that is interpreted to mean a sudden opening up of hitherto closed pulmonary capillaries. The maximal diffusing capacity decreases with age and with certain disease states. The decrease with disease appears to be related to the particular affliction which the disease holds for the lung. For the syndrome "caused by a variety of pathological processes and characterized histologically by alterations of the pulmonary diffusing surface, . . . and physiologically by a reduction in the oxygen diffusing capacity of the lungs," the term "alveolar-capillary block" has been proposed.[18]

SUMMARY

The several functions of the lungs can be divided into certain definite categories for which there are tests whose number is legion, but which, with all their number and complexity, do not replace clinical evaluation of the patient.

Ventilatory impairments are either obstructive, restrictive, or mechanical. The tests, in general, which provide the most information in regard to the performance of the respiratory bellows are the conventional vital capacity, the timed vital capacity, and the maximal breathing capacity. However, in ventilatory impairments, the important consideration is in regard to the adequacy of the alveolar ventilation.

Distribution of inspired air and of mixed venous blood to the alveoli must be uniform if the blood is to be maximally arterialized. Variations in the ventilation/blood flow ratio is a frequent cause of hypoxemia in clinical medicine.

The facility with which the respiratory gases diffuse across the alveolar-capillary membrane can be judged by a study of the arterial blood gases, or by determination of the diffusing capacity of the lung. A determination of the diffusing capacity is helpful in that it supplies information not obtained from simple blood gas studies.

RESUMEN

Las diversas funciones del pulmón pueden dividirse en varias categorías definidas para las que hay pruebas en gran número, pero que con todo y su número y su complejidad no substituyen la valuación clínica del enfermo.

Los trastornos ventilatorios son ya sea obstructivos, restrictivos o mecánicos. Las pruebas que en general proveen de la mayor información respecto del trabajo del pulmón como fuelle son la capacidad vital común, la capacidad vital por segundos y la capacidad respiratoria máxima.

Sin embargo en los trastornos ventilatorios la consideración importante es lo que se refiere a la eficiencia de la ventilación alveolar.

La distribución del aire inspirado y de la sangre venosa mezclada en los alvolos debe ser uniforme cuando la sangre debe ser "arterializada" al máximo. Las variaciones de la relación entre la ventilación y el flujo sanguíneo constituyen la causa frecuente de la anoxemia en medicina clínica.

La facilidad con que los gases respirados se difunden a través de la membrana alveolo-capilar puede juzgarse por el estudio de los gases arteriales, por la determinación de la capacidad de difusión del pulmón. Una determinación de la capacidad de difusión pulmonar es útil porque da información que no se obtiene por el simple estudio de los gases en las muestras de sangre.

RESUMÉ

Les diverses fonctions des poumons peuvent être divisées en certaines catégories précises pour lesquelles il existe de très nombreux tests mais qui, malgré leur nombre et leur complexité, ne remplacent pas l'appréciation clinique du malade.

Les troubles ventilatoires sont obstructifs, restrictifs ou mécaniques. Les tests qui, en général, apportent le plus d'niformations en ce qui concerne la fonction respiratoire sont la capacité theorique, la capacité vitale minute et la ventilation maximale. Cependant, dans les troubles ventilatoires, il faut surtout considérer la bonne qualité de la ventilation alvéolaires.

La distribution de l'air inspiré et du sang veineux mélangé dans les alvéoles doit être uniforme pour que le sang soit artérialisé au maximum. Des variations dans le quotient ventilation-débit sanguin sont une cause fréquente d'anoxémie.

La facilité avec laquelle les gaz reespiratoires diffusent à travers la membrane alvéolo-capillaire peut être jugée par l'étude des gaz du sang artériel, ou par la détermination de la capacité de diffusion du poumon. Une détermination de cette capacité est utile en ce qu'elle apporte des renseignements qui ne sont pas obtenus par la simple étude des gaz sanguins.

ZUSAMMENFASSUNG

Die verschiedenen Lungenfunktionen lassen sich in bestimmte, wohl abgegrenzte Arten aufteilen; es gibt für sie Bestimmungsmethoden, deren Zahl Legion ist. Sie ersetzen bei all ihrer Vielzahl und Kompliziertheit jedoch nicht die klinische Beurteilung des Kranken.

Beeinträchtigungen der ventilatorischen Funktion sind entweder von obstruktiver, einschränkender oder mechanischer Natur. Im allgemeinen sind die Proben, welche die meisten Informationen ergeben, über das Ausmaß des respiratorischen Vermögens, die konventionelle Vitalkapazität, der Atemstoß und der Atemgrenzwert. Es liegt jedoch bei einer Einschränkung der Ventilation der Schwerpunkt der Beurteilung in der Zulänglichkeit der alveolären Durchlüftung. Die Verteilung der eingeatmeten Luft und des gemischten venösen Blutes auf die Alveolen muß gleichmässig erfolgen, soll das Blut maximal arterialisiert werden. Abweichungen in dem Verhältnis von Beatmung zu Durchblutung ist eine häufige Ursache für die Anoxämie in der klinischen Medizin.

Die Leichtigkeit, mit der sich die Atemgase durch die Membran zwischen Alveolen und Kapillaren ausbreiten, läßt sich durch Untersuchung der arteriellen Blutgase beurteilen oder durch Bestimmung des Diffusionsvermögens der Lunge. Eine Ermittlung der letzteren ist insofern eine Hilfe, als die Informationen ermöglicht, die nicht durch einfache Blutgasanalysen gewonnen werden können.

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X-RAY FILM OF THE MONTH

Edited by Benjamin Felson, M.D.

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Clinical Information

A 49 year-old man was admitted to the hospital with complaints of productive cough, slight shortness of breath and occasional night sweats of two months' duration. There was no hemoptysis or history of previous respiratory illness. He had been a moderate smoker for 30 years. Physical examination was not remarkable and there was no cyanosis. Skin tests, cytology and cultures of bronchial washings were negative. On bronchoscopy, there was a thick exudate coming from the superior segment of the left lower lobe. The chest film revealed poorly defined consolidation of the superior segment of the left lower lobe.

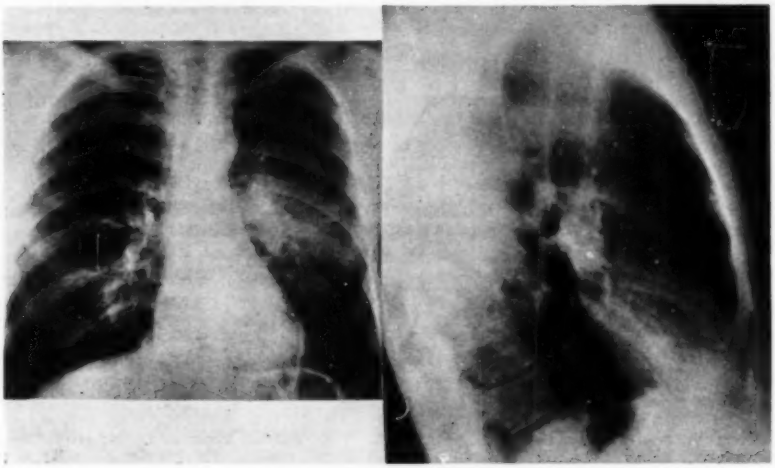

FIGURE 1a: Postero-anterior chest film. FIGURE 1b: Left lateral chest film.

Answer: LIPOID PNEUMONIA

Left pneumonectomy was performed. Examination of the specimen demonstrated consolidation and yellow pus in the superior segment of the left lower lobe with surrounding pleural adhesions. The surgeon felt that the lesion closely resembled that of carcinoma. Microscopically, there was marked fibrosis with acute and chronic inflammation. Lipid-filled histiocytes were present in the alveolar spaces. The diagnosis was organizing lipoid pneumonia. Further questioning of the patient disclosed that for many years he had instilled a mentholated petroleum preparation into his nostrils before going to bed.

*Department of Radiology, University of California Medical Center.

There are no roentgenographic findings which are diagnostic of lipoid pneumonia. Two general appearances are described, the diffuse and the nodular. The former is more common and consists of widespread, ill-defined linear densities which have a "spun glass" appearance. The latter, illustrated by this case, may be well circumscribed or poorly delineated with extension of fine projections into the adjacent tissue. The disease has a predilection for the posterior segments of both lower lobes, more predominantly on the right. The lesion may closely resemble tumor both grossly and roentgenographically. In one series of 35 consecutive cases, nine were operated for suspected tumor. The microscopic appearance is usually diagnostic. A high index of suspicion is the best asset in making the diagnosis.

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with a brief history. Please submit material to: Benjamin Felson, M.D., Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

PULMONARY FUNCTION STUDIES USED TO EVALUATE AIR POLLUTION ASTHMA DISABILITY

High incidence of asthma was noted in the vicinity of the city of Yokohama (in 1946, shortly after the U.S. Armed Forces began their occupation of Japan). The 1946 U.S. Army Hospital, Yokohama, Essential Technical Data Report recorded that the clinicians at that hospital were seeing an unusually large number of patients with asthma. Because of this high incidence of asthma in the area and the dramatic improvement of the patients when moved from there, the disease was popularly called "Yokohama Asthma." Since 1950 the disease has been observed throughout the Kanto Plain (Tokyo-Yokohama region) with increasing frequency. It has become one of the major causes of morbidity among U.S. military personnel and their dependents in the area.

It is apparent from our studies that all of the patients with this disease had marked air flow obstruction. The vital capacities were usually close to normal. The air flow rates in hospitalized patients were considerably worse than those in patients who were seen only in the outpatient clinic. It was observed that many hospitalized patients were seen frequently in the outpatient clinics and had several readmissions to the hospital. Many of these patients were examined at the time of the pulmonary function studies and no wheezing could be elicited. The only evidence of the severity of the underlying disease was the history of marked shortness of breath. External spirometric pulmonary function studies provide a useful and reliable tool to determine objectively the degree of air flow obstruction manifested by shortness of breath in these patients.

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SECTION ON CARDIOVASCULAR DISEASES

Pulmonary Function in the Selection of Patients for Open Heart Surgery*

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Open-heart surgery provides new and definitive operations. The complicated relationship of pulmonary function to heart disease and to previous thoracotomy imposes new obligations in assessing pulmonary function if further surgery is contemplated. If either initial or reoperation is destined to failure because of coexisting and irreversible lung destruction, it is important to know it.

A retrospective look at some of our successes and failures demonstrated some fallacies in our preoperative evaluation. The purpose of this discussion is to relate these experiences and organize the lessons we have learned.

All of the patients in this study had had previous intracardiac surgery. They had either failed to improve or had deteriorated after initial improvement following that intracardiac operation. Ellis' follow-up study of our first 1,000 valvuloplasties for mitral stenosis[1] showed that mild to moderate mitral insufficiency did not alter the late results if mitral stenosis dominated and was corrected. However, dominant regurgitation present or produced by the initial surgery was a major cause of deterioration after valvuloplasty.

Other patients in this study who deteriorated after initial improvement were shown at the time of re-evaluation to have recurrent stenosis. Usually this is due to an inadequate initial operation, but a small number have had recurrent rheumatic valvulitis.

This mixed group with either borderline or frank congestive failure have been re-evaluated with a view to open-heart correction of their valvular defects. These patients had had prior left thoracotomy, were in and out of congestive failure and were known to have extensive pulmonary vascular disease. It was necessary to ascertain the contribution of each lung to overall respiratory function as the original operation had been through the left hemithorax and the approach to the left atrium

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Supported in part by United States Public Health Service Grant No. H-2419.
*Presented at the 26th Annual Meeting, American College of Chest Physicians, Miami Beach, Florida, June 6-10, 1960.
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for open operation was to be through the right side. Unilateral lung function is critical in a patient's course during the immediate postoperative period when voluntary effort is not assisted as it is during the operation.

Previous experience in the evaluation of postoperative pulmonary function,[2] suggested that prior thoracotomy would impose a relatively minor loss of vital capacity rue to the "thoracotomy effect." It was anticipated that there would be a slight shift of function to the unoperated lung, but that the degree of shift would not be of sufficient magnitude to preclude a contralateral thoracotomy.

This report describes the results of a preoperative evaluation of pulmonary function following maximal treatment in patients with prior left thoracotomy requiring reoperation. The influence of the findings on the final surgical plan will be described.

Clinical Material

Eighteen patients were studied, 14 women and 4 men, ranging from 22 to 64 years in age. All had had rheumatic mitral valve disease and had had prior cardiac surgery through left thoracotomy. They were readmitted for study with a clinical diagnosis of mitral stenosis and insufficiency. Five were in Group III and 13 in the Group IV category.[3] All were candidates for open-heart surgery. In addition to the pulmonary function studies reported here, cardiac catheterization, electrocardiograms, serum electrolytes, as well as standard laboratory tests to assess hepatic and renal function were obtained. Clinical evaluation was the combined responsibility of the medical and thoracic surgical services.

Methods of Pulmonary Function Testing

Ventilatory measurements, including maximum breathing capacity, vital capacity, as well as bronchospirometry were performed before surgery.

Ventilatory tests on all patients were performed by the same technician, using the same equipment and methods for all tests.

Maximum breathing capacity was performed with the subject in the sitting position breathing room air for 30 seconds. A direct spirogram

TABLE 1—PATIENTS OPERATED BY OPEN HEART PROCEDURE

					Spirometry				Bronchospirometry							
									Ventilation L./min.				O_2 Cons. ml./min.			
Patient	Age (yrs.)	Ht. (cm.)	Wt. (kg.)	VC (L.)	Per cent pred.	1 sec. VC per cent	MBC (L./min.)	Per cent pred.	Rt.	Per cent total	Left	Per cent total	Rt.	Per cent total	Left	Per cent total
1 D.G.	44	170	56	1.85	60	67	64.8	80	6.8	56	5.4	44	157	52	145	48
2 M.M.	56	157	55	1.50	54	75	43.0	64	3.0	51	2.8	49	118	51	112	49
3 W.McK.	38	177	79	3.40	78	76	121.5	93	3.9	50	3.9	50	224	59	157	41
4 J.R.	43	152	50	1.69	61	76	45.9	64	2.9	44	3.7	56	128	41	184	59
5 H.R.	64	181	61	2.81	73	59	57.0	60	6.8	68	4.0	32	246	63	112	37
6 A.E.	38	175	78	3.03	70	89	108.0	86	6.8	65	2.8	35	302	69	89	31
7 C.S.	23	162	62	2.66	81	61	54.0	57	6.0	64	3.4	36	179	57	134	43
8 E.D.	29	157	43	1.13	36	69	35.0	43	3.7	39	5.7	61	179	53	157	47

was made using a counterbalanced Collins Vitalometer from which the CO_2 cannister had been removed.

The resistance of this equipment was less than 0.1 cm. of water. The maximal value of two efforts recorded at A.T.P.S.* (73 ± 2°) was reported in liters per minute.

Vital capacity was measured directly on a 9 L. Collins respirometer. The best of two efforts with the subject sitting was recorded in liters.

Bronchospirometry was performed on fasting subjects premedicated with 50 or 100 mg. of pentobarbital. All subjects were alert and cooperative. A double-lumen flexible rubber Carlen's catheter was introduced with the aid of a laryngeal mirror. Topical anesthesia was obtained with 0.5 per cent tetracaine hydrochloride (Pontocaine) as an oropharyngeal spray and a 0.25 per cent tracheal instillation.

Correct catheter position was confirmed by auscultation and fluoroscopy. In the supine position, the subject breathed a 35 per cent oxygen-rich mixture from a Collins twin recording spirometer. Two three-minute tracings were obtained at each examination. In many cases, each lung was separately evaluated by clamping the contralateral tubing. Ventilation rate, oxygen uptake, and minute volume were measured. The contribution of each lung as a per cent of the total function was computed.

Results

Four of the 18 patients studied were found not to be candidates for open-heart surgery for reasons not related to their pulmonary function. One was found to have recurrent mitral stenosis by cardiac catheterization. Reoperation was carried out using the "closed" Ivalon® tunnel procedure.[4] Mitral stenosis without regurgitation was found and corrected. Another patient had coronary sinus blood flow studies suggesting severe coronary artery disease. Left heart catheterization indicated no significant stenosis or regurgitation at either the aortic or mitral valve. Pulmonary function was within normal limits. No operation was advised. The remaining two patients were in terminal congestive heart failure and considered inoperable.

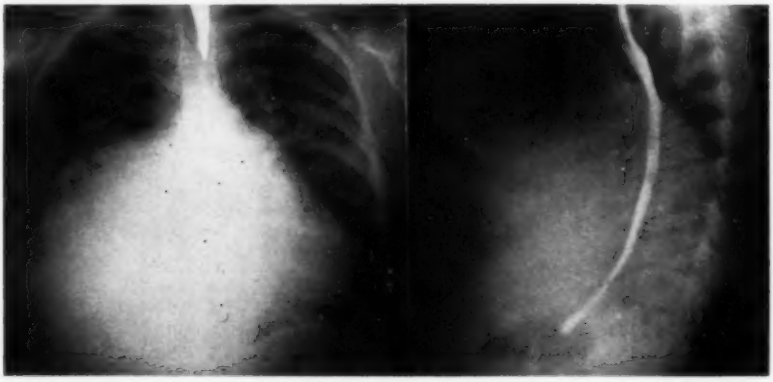

FIGURE 1: Posteroanterior and lateral chest roentgenograms of E. D., patient 8, Table 1. Note giant left atrium.

*Ambient temperature and pressure, saturated with water vapor.

Of the remaining 14 patients, 2 were in Group III and 12 in Group IV of the Harken-Ellis classification.[3] It is emphasized that virtually all of these patients were totally disabled and were on intensive medical therapy. These efforts generally would be regarded as salvage surgery.

These patients have been grouped into three general categories: (1) acceptable for right thoracotomy and open-heart surgery; (2) acceptable for cardiac surgery, but not for right thoracotomy; and (3) unacceptable for surgery.

The *first category* included eight patients who had mild to moderate restrictive ventilatory patterns by routine spirometry (Table 1). As determined by bronchospirometry, four patients (No. 1 - No. 4) showed approximately equal division of function. These individuals, with relatively good over-all function, underwent right thoracotomy and correction of their mitral insufficiency by an open-heart technique. Respiratory insufficiency, either during the intra-operative or postoperative period, was not a problem in their management. Patients 5, 6 and 7 demonstrated a significant inequality of function between the two sides (greater than 65 per cent to 35 per cent). Dominant function was present on the right side. Surgery was carried out on the basis that they had relatively good over-all function, (*i.e.*, VC and MBC were greater than 55 per cent of predicted). Although respiratory insufficiency was not a problem during the operative procedure, it was a significant factor in the postoperative course of two of these patients.

The eighth patient presented a more complex problem. Her x-ray films are shown in Figure 1. The giant left atrium was calculated by planigraphic studies to contain four to five liters of blood. There was definite alteration of the bronchi, particularly elevation of the right main-stem bronchus. This may well have accounted for the disparity between ventilation (39 per cent right, 61 per cent left) and oxygen uptake (53 per cent right, 47 per cent left). In spite of a significant reduction in over-all function, (VC and MBC less than 45 per cent of predicted) right thoracotomy was undertaken. The heart (left atrium) occupied an inordinate part of the intrathoracic space. It was planned to excise much of the left atrium and thus permit better expansion and more adequate ventilation of the right lung. This should have augmented total pulmonary function. This was technically feasible, but maintenance of adequate ventilation was difficult during the operation. Right thoracotomy was per-

TABLE 2—PATIENTS REJECTED FOR OPEN HEART SURGERY (REOPERATION, LEFT THORACOTOMY)

						Spirometry				Bronchospirometry						
										Ventilation L./min.				O_2 Cons. ml./min.		
	Patient	Age (yrs.)	Ht. (cm.)	Wt. (kg.)	VC (L.)	Per cent pred.	1 sec. VC per cent	MBC L./min.	Per cent pred.	Rt.	Per cent total	Left	Per cent total	Rt.	Per cent total	Left	Per cent total
1	C.Y.	50	165	50	1.94	67	81	75.6	100	3.4	67	1.7	33	123	54	101	46
2	S.K.	46	167	66	1.41	47	76	35.1	41	7.2	85	1.3	15	168	88	22	12
3	E.S.	47	157	50	2.08	74	60	64.8	89	4.5	67	2.3	33	157	67	78	33

formed. The giant left atrium compressed the right lung. The patient was placed on cardiopulmonary bypass. The atrium was opened. Much of the redundant auricular wall was excised to reduce the heart volume. The mitral valve was found to be freely incompetent. The mitral insufficiency was repaired, but in so doing the left ventricle presumably ejected air into the base of the aorta. The patient did not regain consciousness. Death occurred 12 hours later presumably due to cerebral air embolus. Even in retrospect this unusual operation seems to have been rational. The defect lay in the complete correction of the mitral insufficiency without perfect air evacuation before closing the heart.

The *second category* consisted of three patients whose pulmonary function studies revealed predominant ventilatory function by the right lung (in excess of 65 per cent), Table 2. Cardiac catheterization studies revealed a significant degree of mitral stenosis. In the light of prior experience, it was believed that these individuals would not tolerate an operation through the right chest which would compromise their dominant hemithorax. These individuals were reoperated through a left thoracotomy using an Ivalon® operating tunnel,[4] for repeat mitral valvuloplasty. Respiratory insufficiency was not encountered during the operative or postoperative period in these patients.

The *third category* consisted of three patients with dominant function remaining on the right side (Table 3). Two demonstrated a function difference in ventilation greater than 70 per cent to 30 per cent while the third had a 65 per cent to 35 per cent division for oxygen uptake with an essentially equal partition of ventilation. This last individual had a giant left atrium as did patient 8 in the first category. These individuals were Group IV patients (refractory congestive failure). Diminished cardiac reserve and inequality of pulmonary function were the contraindication to surgery.

Discussion

The limitations of pulmonary function tests must be recognized in evaluating this study. Variations in motivation, errors of measurement, changes in respiratory muscle capabilities and changes in the lung itself account for variations in vital capacity and maximum breathing capacity. Regardless of these factors, previous experience[3] led us to expect only moderate restriction of the over-all function without marked discrepancy of ventilation due to previous thoracotomy. Three patients (not included in the original 18 patients) with equivalent degrees of mitral valvular disease and heart failure, but without prior thoracotomy, were studied. These showed normal division of function between the lungs. The influence of heart disease and congestive failure therefore did not appear to alter the normal partition of ventilatory function.

TABLE 3—PATIENTS REJECTED FOR SURGERY

						Spirometry				Bronchospirometry							
										Ventilation L./min.				O_2 Cons. ml./min.			
	Patient	Age (yrs.)	Ht. (cm.)	Wt. (kg.)	VC (L.)	Per cent pred.	1 sec. VC per cent	MBC (L./min.)	Per cent pred.	Rt.	Per cent total	Left	Per cent total	Rt.	Per cent total	Left	Per cent total
1	A.M.	41	161	44	1.38	47	78	43.2	59	6.15	68	2.79	32	168	61	107	39
2	V.G.	51	165	40	1.45	50	69	27.0	42	10.21	76	3.12	23	336	71	134	28
3	G.C.	37	180	91	2.30	53	60	42.9	38	4.82	53	4.25	47	250	65	135	35

While all of 18 patients had mild to moderate restriction of their over-all pulmonary function, only four showed an essentially equal partition. The remaining ten patients had significant differences in their unilateral lung function. Three of these ten were not accepted for operation. Each of these individuals demonstrated dominant function in the right hemithorax and all had severe mitral regurgitation. These individuals would certainly not have tolerated a right thoracotomy. The combination of marginal pulmonary function and advanced congestive heart failure precluded operation. These decisions were made before a technique of reoperation for mitral insufficiency through the left hemithorax was developed.

An additional three patients did not have open-heart surgery, but were reoperated through the left chest. These patients with marginal pulmonary function, dominant on the right side, had significant degrees of residual or recurrent mitral stenosis. The necessity to preserve the dominant hemithorax dictated an alteration of the surgical approach.

Four patients were accepted for an open procedure through the right chest in spite of inequality of pulmonary function. Three of the four presented problems in handling respiratory insufficiency either during the intraoperative or early postoperative period.

The foregoing experience has led to the development of an alternative approach, through the left chest wall, to open reoperation for the correction of mitral valve disease. This affords better exposure of the mitral valve and a better direct valvuloplasty. It does have the disadvantage of operating through a field of adhesions in an individual heparinized for by-pass.

The primary consideration, however, is that adequate ventilatory studies have improved patient selection, helped in clarifying an inoperable group and stimulated the development of a more appropriate operation through the left hemithorax in order to adapt to this problem of compromised pulmonary function.

SUMMARY

1. Thoracotomy incident to cardiac surgery causes a variable restriction on pulmonary function. Bronchospirometric studies have shown that the predominant loss is due to restrictive disease in the operated hemithorax. Routine ventilatory studies will not ascertain this unilateral difference in function.

2. Pulmonary function testing in patients under study for repeat cardiac surgery distinguished three groups of patients:

I. Those whose respiratory limitations contraindicated further surgery.

II. Those with marginal function acceptable for surgery if it did not compromise the lung performing major function.

III. Those whose respiratory status permitted open-heart surgery through either hemithorax.

3. The unoperated hemithorax has been established as essential to survival in some patients. A surgical approach to the mitral valve through the previously operated hemithorax (left side) has been developed and used.

RESUMEN

1. La toracotomía que se hace con motivo de cirugía cardiaca causa una restricción variable de la función pulmonar. Los estudios broncoespirométricos han demostrado que la pérdida que predomina es debida a la enfermedad restrictiva en el lado operado del tórax. Los estudios de ventilación no aclaran esta diferencia unilateral de la función.

2. Los estudios funcionales en enfermos que se han estudiado por cirugía reiterada del corazón distinguen tres grupos:

I. Aquellos cuyas limitaciones respiratorias contraindican hacer nueva cirugía.

II. Los que tienen función marginal aceptable si no comprometieron la mayor función del pulmón.

III. Los que tienen una condición respiratoria que permite la cirugía de corazón abierto en cualquier lado.

3. El hemitorax no operado se ha establecido como esencial para la sobrevida en algunos enfermos. Se ha ideado una técnica quirúrgica para el tratamiento quirúrgico de la mitral a través del lado previamente operado (lado izquierdo) y tal técnica se ha usado.

RESUMÉ

1. La thoracotomie qui accompagne les opérations cardiaques provoque une atteinte variable de la fonction pulmonaire. Des études bronchospirométriques ont montré que la perte prédominante est imputable à une diminution fonctionnelle de l'hémithorax opéré. Les études fonctionnelles de routine ne peuvent faire la preuve de cette différence unilatérale dans la fonction.

2. L'étude de la fonction pulmonaire chez les malades en observation pour des opérations cardiaques répétées permet de distinguer trois groupes de malades:

I. ceux dont les limitations respiratoires contre-indiquent une opération ultérieure;

II. ceux dont la fonction pulmonaire marginale est acceptable pour une opération, si celle-ci ne compromet pas le poumon fournissant la fonction majeure;

III. ceux dont l'état respiratoire permet une chirurgie à coeur ouvert par l'un des hémithorax.

3. Il a été établi que l'hémithorax inopéré est essentiel à la survie chez certains malades. Une tentative chirurgicale sur la valvule mitrale par l'hémithorax antérieurement opéré (côté gauche) à été pratiquée.

ZUSAMMENFASSUNG

1. Eine Thorakotomie als Zwischenfall bei Herzoperationen führt zu einer verschieden starken Einschränkung der Lungenfunktion. Bronchospirometrische Untersuchungen haben ergeben, daß der hauptsächliche Verlust die Folge einer beschränkenden Erkrankung des operierten Halbthorax ist. Die üblichen Atemfunktionsprüfungen werden diese einseitige Differenz nicht ermitteln.

2. Lungenfunktionsprüfungen bei Kranken, die wegen wiederholter Herzoperationen unter Beomachtung stehen, ließen drei Gruppen von Patienten unterscheiden.

I. Solche, deren eingeschränkte Atmung eine Kontraindikation für weitere Eingriffe ist.

II. Solche mit Grenzwerten, die zur Operation zugelassen werden können, wenn diese nicht die größere Leistung aufweisende Lunge beeinträchtigt.

III. Solche, deren resepiratorische Verfassung Operationen am offenen Herzen bei jedem Halbthorax zuläßt.

3. Der von der Operation nicht betroffene Halbthorax wurde bei manchen Patienten als wesentlich für das Überleben ermittelt. Es wurde ein chirurgischer Zugang zur Mitralklappe auf dem Weg durch den vorher operativ eröffneten Halbthorax (linke Seite) entwickelt und benutzt.

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VASODILATING DRUGS AND CORONARY BLOOD SUPPLY

Treatment of localized myocardial ischemia depends upon addition of arterial blood by way of intercoronary arterial communications. Pentaerythritol tetranitrate adds 0.81 cc. per minute to the ischemia circumflex area of the dog heart. Amyl nitrite adds 0.98 cc. per minute to the ischemic circumflex area of the dog heart. Alcohol decreases intercoronary flow by 1.93 cc. per minute. Increased intercoronary flow resulting from drug action is temporary. Addition of 0.81 cc. per minute as produced by pentaerythritol tetranitrate did not reduce mortality or infarct size following test coronary artery ligation in a series of 21 experiments.

Leighninger, D. S., Rueger, R., and Beck, C. S.: "Effect of Pentaerythritol Tetranitrate, Amyl Nitrite and Alcohol on Arterial Blood Supply to Ischemic Myocardium," *Am. J. Cardiol.*, 7:533, 1961.

IMPAIRMENT OF DIFFUSION IN MITRAL STENOSIS

Methods of determining alveolar diffusing capacity and its clinical significance in connection with pathologic physiology of mitral stenosis and effect of commissurotomy are described. It was shown that the PO_2 difference between alveolar gas and arterial blood (A-a gradient) depends upon various factors such as membrane component, venous admixture component and hyperventilation. Pulmonary diffusing capacity (DLco) was measured by CO method. It was found the impairment of diffusing capacity (or increased A-a gradient) mainly due to disturbance in membrane component was irreversible with commissurotomy, while that mainly due to disturbance in venous admixture component or due to hyperventilation was comparatively reversible with commissurotomy. In the cases with decreased DLco, a marked thickening of the basement membrane on the blood-air pathway was revealed by electron microscope.

In deciding the indication of commissurotomy for mitral stenosis, determination of impairment of diffusing capacity has great significance as well as pulmonary arterial pressure, capillary pressure, vascular resistance and A-a gradient.

Miyamoto, S. *et al.*: "Impairment of Diffusion in Mitral Stenosis," *Lung and Heart (Japan)*, 8:3, 1961.

The Use of Chlorothiazide or Hydrochlorothiazide with Reserpine in the Office Treatment of Hypertension

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Introduction

Essential hypertension is an important problem in the office practice of medicine. Twenty to 25 per cent of the adults in the United States are affected.[1] This disease has serious implications in cardiac, cerebrovascular and renal degeneration. According to insurance statistics, the height of the blood pressure may be correlated with life expectancy. Yet, prior to the past decade, treatment of hypertension was almost primitive. Ten years ago mild to moderate cases were treated with dietary changes, weight loss, rest and mild sedatives. A few drugs were employed, such as theophylline, nitrites, thiocyanates and veratrum preparations. These drugs were effective for only short periods or at doses which were toxic. The largest proportion of these cases was helped little and the disease would continue to progress. Severe cases were treated with extreme restriction in dietary salt and protein (rice diet) or sympathetic nervous system surgery.

Since 1950, a number of potent antitensive agents have been introduced including hydralazine, the ganglionic blocking agents, new veratrum derivatives and the rauwolfia preparations. These, singly and in combination, have been employed successfully in many patients including severely affected ones. Their use, however, involves complicated regimens, frequent and careful observation, development of tolerance and many annoying or even dangerous side effects. Patients with mild or moderate hypertension usually have few or no symptoms and do not happily accept these agents. Yet treatment is necessary because of the prognosis of their disease. What is needed, therefore, is a regimen that is acceptable to the patient with simplicity and relative freedom from side reactions and which can be continued with good results for many years. The synthesis of chlorothiazide[2] and hydrochlorothiazide[3] and their employment in the management of hypertension[4-6] promises to be a hallmark of achievement in medical therapeutics. Several workers have noted the synergistic effect of the rauwolfia derivatives and the benzothiazides in lowering elevated blood pressure[6-8] and it is this combination of agents which we selected to use in our study.

Methods and Materials

For this study, 60 patients with fixed essential hypertension were chosen from our private practice of medicine. Records were available for these patients dating back in many instances 10 to 30 years. All but a few were known in the office for more than a year. This was a great advantage in controlling our study in that patients with intermittent, labile hypertension or patients with pressures elevated temporarily due to a current stressful situation could be eliminated. Also patients that were known to do well with mild sedation and reassurance were not in-

cluded. All patients were subjected to a complete physical examination prior to the study. Electrocardiograms, chest x-ray examinations and urinalyses were done routinely. Blood urea nitrogen determinations were secured in most cases, especially when indicated by suggestive urine findings. The majority of the patients including all of the younger patients and other patients with suggestive signs or symptoms were hospitalized at some time prior to the study to eliminate specific causes of hypertension such as renal disease, pheochromocytoma and coarctation of the aorta.

The study was started initially with chlorothiazide and reserpine in early 1958. When hydrochlorothiazide became available, it was substituted in most of the patients. Later, a tablet containing hydrochlorothiazide, reserpine and potassium was given to 30 of the patients. The patients presented have been followed from two to 30 months on the drugs. Many of the patients had been on reserpine prior to this study. They were continued on this and a thiazide derivative added to the regimen. The dosage of each of the two drugs was adjusted independently in each patient by giving extra reserpine in addition to that already in the combined tablets when necessary. In the majority of patients, the amount of reserpine in the combined tablets seemed sufficient. Some patients required extra reserpine initially, but after several weeks the dose could be reduced. The patients were seen three days after being started on the regimen; then at one-week intervals. When the pressures were stable and side effects, if any, controlled, the patients were checked every two weeks. The tablets were carefully counted at each visit to determine if the medication was being taken as directed. The medication was given the same degree of reassurance that all previous remedies (usually without success) had been prescribed. The patients rested in the office in a sitting position for at least one half hour prior to the recording of the sitting blood pressure by the office nurse. The pressures were checked 15 minutes later by the physician to determine any marked lability.

No system of placebos was instituted, but in a group of patients the thiazides were interrupted for one of the following reasons:

1. development of side effects
2. the patient did not return for a prolonged period of time for various reasons
3. by design on part of investigator to test the efficacy of the medication in some of the moderate, uncomplicated cases.

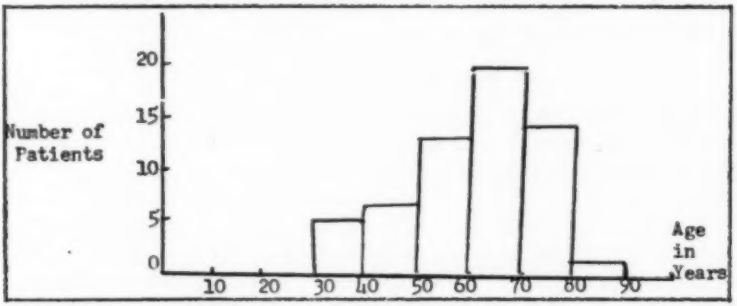

FIGURE 1: Age distribution of patients.

In the latter two groups, the effect of reinstitution of the medication could also be demonstrated.

All of the patients were on a salt-poor (not "salt-free") regimen. They were instructed to take at least 8 ounces of citrus or tomato juice daily.

Results

The findings of this study are summarized in Figures 1, 2, 3, 4, and 5. The doses of medication used were those which seemed optimum to the investigators, *i.e.*, those lowest doses that gave as near to maximal blood pressure reduction without side effects. In seven instances, the thiazides had to be discontinued. This was most frequent early in the study and often due to patient rejection. This will be discussed more fully in the section on side effects. Most of these patients who were previously on reserpine and one who had a sympathectomy ten years before showed good blood pressure reductions within a week of adding a thiazide to the regimen. Those who had not been on reserpine usually required two to five weeks for near maximal response. This probably represents the latent period in the action of reserpine and could be decreased by adding additional reserpine initially. Some patients responded in a few days who had not taken reserpine prior to the study.

The thiazide derivative proved quite successful as an adjunct with reserpine in the management of mild to moderately severe essential hypertension. There were only four cases (6.7 per cent) in whom the regimen failed to produce a significant blood pressure response. In another seven patients (11.6 per cent), the thiazides were withdrawn. With more experience in the administration of these agents and good patient cooperation, the figure could be reduced to a minimum. With most individuals who experienced side effects, they were mild, transient and simple to control. A glance at Figure 4 demonstrates the greater effectiveness of combined therapy over reserpine alone. This is not completely valid since milder cases, well controlled on reserpine, were not included in this study. There seemed to be little difference in the effectiveness of chlorothiazide and hydrochlorothiazide. However, 50 mg. of hydrochlorothiazide appeared more effective than 500 mg. of chlorothiazide and probably as effective as 750 mg. of chlorothiazide. There appeared to be no development of tolerance to the regimen though some patients were followed over two years. Interrupting the treatment allowed rapid rise

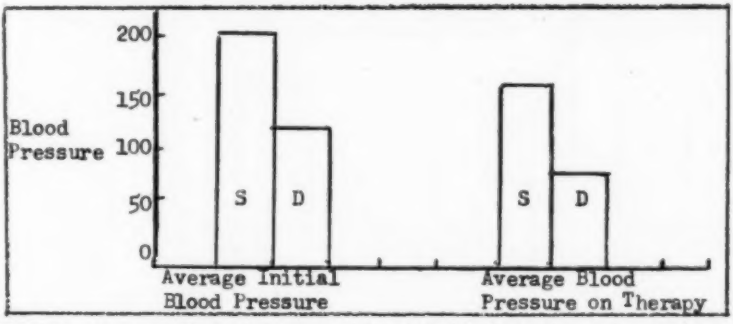

FIGURE 2: Average effect of therapy with a thiazide derivative and reserpine combined.

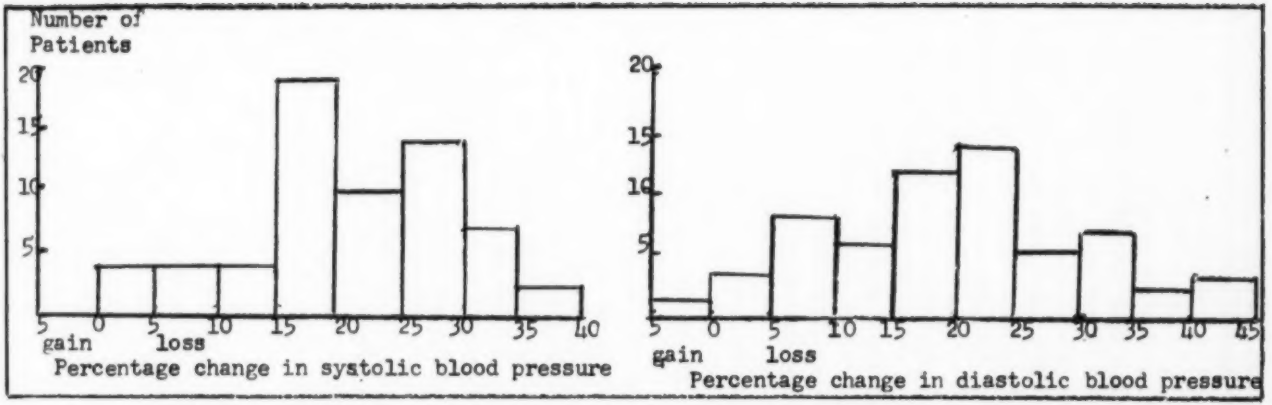

FIGURE 3: Distribution of individual changes in pressure by using combined therapy.

in pressure and starting treatment again invariably produced the previous good results. The addition of KC1 to the regimen did not appear to effect the blood pressure. *It was our impression that the vast majority of the patients could be controlled with 25 mg. or 50 mg. of hydrochlorothiazide and 0.125 mg. of reserpine combined in one or two tablets daily without side effects.*

Side Effects

Twenty of the 60 patients experienced some side effects from the regimen. The most common complaint was that of weakness. This usually developed in three to 10 days. Five patients had actual syncope. One fell, fracturing several ribs, causing pneumothorax. This syncopal episode occurred after three days on 150 mg. of hydrochlorothiazide and 0.375 mg. reserpine. Later, with reduced dosage, the patient tolerated the drugs well and is now maintained normotensive without discomfort. For the majority, the dizziness or weakness was transient and easily controlled by reducing the dose and/or adding extra potassium to the diet. This extra potassium was given in the form of enteric-coated potassium chloride 1 to 4 gm. daily and by urging the patient to drink large amounts of citrus or tomato juice. Later, tablets incorporating 8 grains of KC1 with hydrochlorothiazide and reserpine were given. Even with these, it was necessary at times to give additional potassium. Often it was possible to discontinue the KC1 after a while without recurrence of weakness. One experienced anorexia. This diminished when the dose was decreased. The patient tolerated the mild anorexia because of the excellent result on his blood pressure. The medication was withdrawn in seven because of side effects. In four of these cases, the patient refused to accept even a reduced dose. Three more did not seem to tolerate any without weakness. Many workers[5,6,9] have demonstrated that the thiazides can cause prolonged reduction in serum potassium levels. It has also been shown that potassium deficiency may cause renal tubular changes.[10] For this reason, we did frequent urinalyses and when suspicious, blood urea nitrogen determinations during this study. No patient exhibited change in urinary findings during this time. Four who had

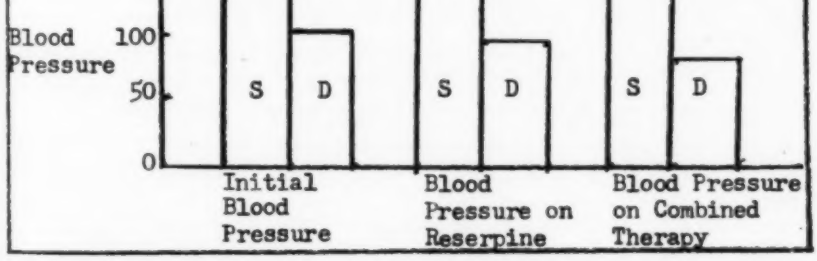

FIGURE 4: Pressure changes by using combined therapy as compared to reserpine alone.

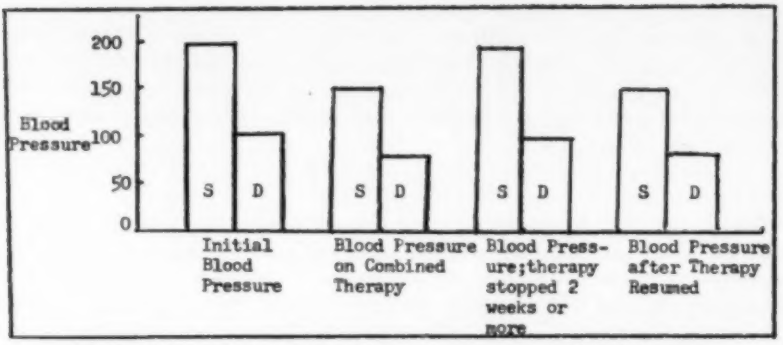

FIGURE 5: Effect of interrupting and resuming combined therapy.

been well maintained on digitalis showed signs of toxicity soon after starting the thiazides. One with auricular fibrillation developed bradycardia. The other three with normal sinus rhythm showed numerous extrasystoles. They were all controlled by reducing the digitalis and thiazide dose and by adding extra potassium to the diet. No idiosyncrasy such as skin eruption or blood dyscrasia was produced in our patients.

Discussion

Rauwolfia derivatives such as reserpine probably decrease blood pressure by increasing blood vessel caliber. This is thought to be accompanied by reduction of sympathetic activity by blocking of afferent impulses centrally.[11] Thiazide derivatives are thought to effect a decrease in pressure by reducing blood volume by diuresis.[12] A combination of these two agents with their different effects on hemodynamics has produced a regimen which appears to be quite successful in the office management of mild to moderately severe essential hypertension over prolonged periods of time. The drugs are effective together in relatively low doses and on a simple schedule (once stabilized) which is readily accepted and easily followed by the patient. This combined therapy is more effective than reserpine alone. Moreover many patients who previously were unable to tolerate antitensive doses of reserpine because of such side effect as depression, irritation of peptic ulcer, diarrhea, insomnia and nasal stuffiness were able to accept the smaller doses of reserpine in this regimen with good result and no recurrence of their previous toxic symptoms.

This regimen served a dual purpose in patients with hypertensive heart and edema. These patients required far fewer mercurial injections. They also experienced far fewer episodes of paroxymal nocturnal dyspnea. This was welcomed both by patient and physician.

SUMMARY

1. Sixty patients with mild to moderate benign essential hypertension were selected from a private office practice of medicine and placed on a regimen of antitensive therapy including reserpine and a benzothiadiazine for two to 30 months.

2. This combined therapy produced significant blood pressure reduction in all but four (6.7 per cent) patients.

3. In seven more patients, the drug was withdrawn because of side effects. This figure could be greatly reduced with experience in use of the drug and patient cooperation.

4. A total of 20 experienced side effects. Most were mild and easily controlled. In none was there severe or permanent toxic effect.

5. It was concluded that this regimen was successful and practical for prolonged administration in mild to moderately severe benign essential hypertension.

ACKNOWLEDGMENT: The chlorothiazide and hydrochlorothiazide and reserpine used in this study were provided by the Merck, Sharp and Dohme Co. in combined tablets available as Diupres, Hydropres 25, Hydropres 50, and Hydropres with potassium.

RESUMEN

1. Se escogieron sesenta enfermos con hipertensión benigna moderada y esencial, de la práctica privada y se colocaron bajo un régimen de tratamiento antitensivo incluyendo la reserpina y una tiazida por dos a 30 meses.

2. Esta terapia combinada produjo considerable descenso de la presión en todos menos 4 (6.7 por ciento) de los enfermos.
3. En otros siete enfermos la droga hubo de retirarse por los efectos colaterales. Esta cifra podria ser grandemente reducida con la experiencia en el uso de la droga y con la cooperación del enfermo.
4. Se observó un total de 20 efectos colaterales. La mayoria son moderados y faciles de dominar. En ninguno hubo efecto toxico grave o permanente.
5. Se concluye que este régimen es util y practico para la administración prolongada en la hipertensión moderada benigna esencial.

RESUMÉ

1. Soixante malades atteints d'hypertension essentielle bénigne, dont le degré d'atteinte était de faible à modéré, furent choisis parmi la clientèle privée et soumis à un régime de traitement antitensionnel comprenant la réserpine et le thiazide pendant une période allant de deux à trente mois.
2. Ce traitement associé produisit une réduction nette de la pression sanguine chez tous les malades sauf quatre (6.7%).
3. Chez sept autres malades, le produit fut cessé à cause des complicatations qu'il provoque. Ce chiffre pourrait être grandement réduit avec l'expérience que l'auteur a maintenant du produit et grâce à la collaboration du malade.
4. Un total de 20 malades a subi des effets toxiques. La plupart furent faibles et aisément jugulés. Dans aucun cas il n'y eut d'effet toxique grave ou permanent.
5. L'auteur conclut que ce traitement fut satisfaisant et pratique por une administration prolongée dans l'hypertension essentielle bénigne, avec atteinte faible ou modérément grave.

ZUSAMMENFASSUNG

1. 60 Kranke mit leichter bis mässig schwerer gutartiger essentieller Hypertension wurden aus einer internistischen Privatpraxis ausgewählt und einer zwei bis 30 Monate lang dauernden antihypertonischen Therapie unterzogen-einschliesslich Reserpin und Thiazid.
2. Diese kombinierte Therapie bewirkte eine wesentliche Blutdrucksenkung bei allen-außer 4 Patienten (6.7%).
3. Bei 7 weiteren Kranken wurde das Medikament abgesetzt wegen Nebenerscheinungen. Diese Zahl liesse sich aber beträchtlich reduzieren, bei entsprechender Erfahrung im Gebrauch des Mittels und Mitarbeit des Patienten.
4. Bei insgesamt 20 Fällen kamen Nebenwirkungen vor. Die meisten waren gering und leicht zu beherrschen. In keinem Fall gab es schwere oder anhaltende toxische Effekte.
5. Es läßt sich der Schluß zeihen, dass dieses therapeutische Vorgehen erfolgreich war und für einc sich über lange Zeit erstreckende Anwendung bei leichten bis mittelschweren Fällen gutartiger essentieller Hypertension geeignet ist.

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Rehabilitation of the Coronary Thrombosis Patient

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The problem of rehabilitating the patient who has suffered a coronary thrombosis has many facets and complexities. The physical experience may be new, but some of the mental and emotional experiences are by no means the patient's first ones. Most often he has become familiar with this disease as it affected a parent, close relative, or friend. He has probably read an account of this disease in *Reader's Digest,* or another periodical or has seen a television program, and the chances are that these have been dramatic portrayals, because anything less than sensational would hardly attract notice in these communication media. A person who has witnessed or read of such an experience often considers himself a minor authority on the subject, and is likely to present his dramatic story at social gatherings. When, to this limited educational experience are added a crushing chest pain, injections, an oxygen mask, a hospital bed, bottles and tubes of fluids, venipunctures, whispered orders of doctors to nurses, and the concerned, worried looks of the nearest of kin, it is little wonder that the patient who has suffered a coronary thrombosis is both a physical and emotional wreck, faced in his own mind with physical suffering which will end in either death or invalidism. With this in mind, it becomes obvious that the rehabilitation process should really have begun years before the coronary thrombosis. The whole problem might be divided into three phases as follows:

1. Preventive Medicine.
   (a) Concerning the contributory causes of coronary thrombosis.
   (b) Education of the public.
2. The conduct of therapy of the acute phase of coronary thrombosis.
3. Programming the patient's future.
   (a) Medical care.
   (b) Emotional and physical stresses.

1. Preventive Medicine

Regardless of any physician's individual beliefs and theories, certain general statements may be made about etiologic factors in myocardial infarction. Hereditary factors may be important, but we have no control over these. It is fairly safe to say that we Americans eat too much animal fat, in many instances we eat too many calories, live a highly mechanized existence in which we exercise too little, and live by time schedules which keep us too tense. It is not unreasonable to feel the sum total of all these factors contribute to biochemical changes which directly or indirectly influence blood pressure, blood vessels, and blood clotting. It is not unreasonable to feel that we as physicians should be able to educate the public in the basic principles of good health and good care, and in this way reduce the number of patients requiring rehabilitation.

No discussion of rehabilitation of the coronary thrombosis patient can be complete without a consideration of chemical approaches to the prevention and treatment of atherosclerosis and coronary thrombosis.

The use of anticoagulants initiated active therapy in a disease which heretofore had been left to the healing powers of nature. The coincident interest in the relationship of cholesterol, neutral and saturated fats to atherosclerosis and thrombus formation gave impetus to biochemical investigations which implicated alpha and beta lipoprotein ratios, cholesterol-phospholipid ratios, low density S-F lipoproteins, and androgens as contributory factors. The scope of this presentation does not permit any detailed discussion of these factors, but I should like to take this opportunity to call attention to the theory of deficient output of heparin by the liver, and to stimulate a greater interest in the long-term use of heparin. There is by now sufficient evidence, in the literature and in my own studies over the past six years, to indicate that heparin is superior to the oral anticoagulants because of its clearing factor; its ability to convert the low density lipoproteins to high density lipoproteins; to increase alpha-lipoproteins, and reduce beta-lipoproteins; and to reduce the sticky factor of red cells. By contrast, the oral anticoagulants act merely as anticoagulants without any of the other beneficial properties attributable to heparin. Although the cost of oral anticoagulants is admittedly less, the cost of heparin is not much greater than that of the oral anticoagulants and prothrombin time determinations. The greater value of heparin far outweighs the slightly higher cost. With some of the newer preparations available, pain is minimal with the parenteral administration of heparin.

2. The Conduct of Therapy

It is not my intention to discuss the actual treatment of a patient, but rather the manner in which we go about it. The powers of concentration and memory of the conscious patient during his ailment are amazing, as are his shrewd tactics in gleaning information. A constant awareness of this fact should help us to protect the patient from obtaining information he shouldn't have, and should instill in us a sense of caution in selecting the proper words, the proper tone of voice, and a casual manner in the patient's presence. It is necessary for the physician to maintain a calm and reassuring attitude. The nurses and technicians must be equally cautious in choosing words, in giving information, or withholding information. Refusing to give information can be disastrous to the patient's emotional balance and it may be better to give partial truths than no information at all. This, too, has its limitations, because it is incumbent upon the physician to carry out any promises he makes, and to instill in the patient the confidence that the privileges he receives are in keeping with the progress he has been told he is making. I have found it to be much more satisfactory to tell a patient that his privileges will depend upon the progress of a blood test, which is a scientific determinant, than to tell him that they will depend upon my opinions.

3. Programming the Patient's Future

This final phase of rehabilitation is probably the most difficult of all because patient and doctor are now separated. The patient is no longer under the physician's direct control, and his behavior and judgment are influenced by how much or how little instruction he was given by his

physician. Up to this point, the physician's problems have been concerned with active therapeutics with specific indications for anticoagulants, digitalis, diuretics, and finally the activities within the confines of a hospital room or corridor. Now the process of education takes on a more active form. It becomes necessary to explain to the patient that he has been driving along the road of life too carelessly, and too speedily, and has been fortunate enough to survive an accident. In keeping with nature's usual manner of handling an injury, a healing process is taking place with the formation of a scar which will remain and which may be visible on an ECG like the scar of any other injury. Since this injury occurred in an organ which cannot be put at complete rest, but must continue in motion 24 hours a day, the work load on the heart must be re-evaluated in the light of its capacity or reserve.

It is important that the patient be made to recognize that the changes in his way of life are not necessarily toward a subnormal existence, but rather toward an ideal existence befitting all normal people of his age. This is the way he should have been living *before* his coronary thrombosis. If he had, the coronary thrombosis might not have occurred. The period of convalescence will depend upon the extensiveness of the infarction, the state of cardiac compensation and laboratory estimates of the completeness of healing. A warm, equable climate is preferable during the convalescent period, because it allows the patient freedom from heavy winter clothing, and also makes it possible for the patient to resume mild muscular activity in the form of short walks. A graduated regimen makes it possible to overcome some of the weakness and easy fatiguability arising from inactivity and poor muscular tone. Sometimes the weakness is a manifestation of a reactive depression which may require electroshock therapy. In general, moderation in all activities should be recommended rather than numerous restrictions. Each case presents an individual problem from mental, physical, and economic standpoints. Work classification units are now in existence in many cities. These consist of a cardiologist, psychiatrist, and social worker who work together in a coordinated effort to rehabilitate the cardiac patient. Walking, golfing, fishing, and swimming should be encouraged in the absence of cardiac decompensation or angina pectoris. Sexual intercourse with or without a prophylactic dose of nitroglycerin may be permitted.

Return to some form of gainful occupation is possible in most instances. Very few, probably only one out of 300 or more patients, is unable to do some kind of work. The former occupation and the physical status after recovery will in great part determine whether the patient can return to his previous kind of work or whether a new type of occupation will be necessary. One should not overlook the effects of domestic problems and the influences of various types of insurances upon successful rehabilitation.

SUMMARY

Rehabilitation of the patient who has suffered a coronary thrombosis is an all-encompassing problem embracing medical, medico-legal, social, emotional, physical, and economic problems.

RESUMEN

La rehabilitación del enfermo que ha sufrido una thrombosis coronaria es un problema muy amplio que incluye problemas médicos, médico-legales, emocionales, físicos y económicos.

RESUMÉ

La réadaptation du malade qui a souffert d'une thrombose coronarienne est un vaste problème embrassant les domaines médical, médico-légal, social, émotionnel, physique et économique.

ZUSAMMENFASSUNG

Die Rehabilitation des Patienten, der eine Coronar-Thrombose erlitten hat, ist ein allumfassendes Problem, das ärztliche, gesundheitsgesetzgeberische, soziale, emotionelle, physikalische und wirtschaftliche Probleme in sich schließt.

CHILDHOOD TUBERCULOSIS: CLINICAL VALUE OF THE ELECTROPHORETIC PATTERN OF THE SERUM PROTEINS

The blood serum protein fractions of 138 children with tuberculosis were analyzed by paper electrophoresis serially over a period of many months. Many manifestations of tuberculous infection were studied. The group was divided into 11 categories ranging from healed or arrested tuberculous disease to various stages of activity. The serum protein fractions were evaluated in terms of prognosis, type of tuberculous disease, effect of intercurrent infection and age of patient. It was found that the greatest changes occurred in the gamma-globulin and albumin fractions in reciprocal relation. With the exception of tuberculous meningitis, the increase in gamma-globulin usually corresponded to the severity of disease. Albumin was correspondingly decreased and was low even in tuberculous meningitis. Both fractions approached normal levels as the patients improved. The greatest deviation from normal was seen in patients with miliary tuberculosis and those with pleurisy with effusion. Here the gamma and alpha$_2$-globulins were very high and the serum albumin was low. The alpha$_2$ fraction was elevated in children with more severe disease, including tuberculous meningitis; with clinical improvement, it returned to normal more rapidly than the gamma. A rise in the beta-globulin fraction suggests caseation.

Nemir, R. L., Zitrin, C. M., Tsouros, P., and Melly, E.: "Childhood Tuberculosis: Clinical Value of the Electrophoretic Pattern of the Serum Proteins," *Pediatrics*, 27:54, 1961.

IMPORTANCE OF INVESTIGATING GLUTAMINO-OXALOACETIC TRANSAMINASE IN THE DIAGNOSIS OF MYOCARDIAL INFARCTION

The author conducted investigations of glutamino-oxaloacetic transaminase by the colorimetric method in 42 myocardial infarction cases, as well as in patients suffering from stenocardia, chronic coronary insufficiency, pneumonia, disturbances of cerebral circulation and comatous conditions. There was seen a 1.8 to 10-fold rise in the activity of transaminase in comparison with the initial level during the first three to five days of affection with myocardial infarction. In chronic coronary insufficiency and pneumonia, the transaminase activity underwent no essential changes. In two of 13 patients with cardiac failure and in one of five patients with disturbance of cerebral circulation, the level of transaminase was slightly above normal.

Special attention is attracted to the particular value of transaminase determination in the diagnosis of myocardial infarction, especially when there is an atypical electrocardiogram in cases of repeated and microfocal myocardial infarctions.

Trushinsky, Z. K.: "The Importance of Investigating Glutamino-Oxaloacetic Transaminase in the Diagnosis of Myocardial Infarction," *Clin. Med. (USSR)*, 39:119, 1961.

The Advantages and Disadvantages of Using Heparin as the Sole Anticoagulant During the First Thirty Days After Acute Myocardial Infarction

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There are a number of opinions on what anticoagulants should be used to treat acute myocardial infarctions and how. The use of heparin for the first 48 to 72 hours while the oral anticoagulants are establishing a suitable prolongation of the pro-thrombin time is a common practice. It has been our impression that the use of heparin for the *entire* hospitalization, usually thirty days, provides a more effective mode of anticoagulation. Clinically we feel "safer" using heparin, both for adequate anticoagulation and the lack of complications. There is evidence to support our clinical impression.[1,2]

Dosage and Administration

Initially, we usually give heparin 100 mg. intravenously. This is followed in four hours by 75 mg. heparin intramuscularly. The intramuscular heparin is continued every six to eight hours at 75 to 100 mg. until the following morning. At that time the patient is started on a concentrated form of aqueous heparin administered subcutaneously. The dosage used thereafter is from 100 to 150 mg. every 12 hours and this is continued for the entire hospitalization.

This dosage has been shown to produce adequate prolongation of clotting.[3] Clotting times are not done and this has proved to be quite safe. If desired, a control Lee-White clotting time can be done and another Lee-White can be done at either 12 or 24 hours after the heparin injection. Occasionally it is found that one subcutaneous injection daily is sufficient to produce continued prolongation of the clotting time.

The site of administration should be varied. The best sites are: suprapubic fat pad, the flanks and along the inferior border of the pectoral muscles. These can be rotated judicially.

The concentrated heparin is administered in a tuberculin syringe, using a No. 25 or No. 26 one-half inch needle. A small amount of air is left in the syringe in order to clear the needle of heparin. The skin fold is grasped between two fingers and pressure applied until the area is blanched. The heparin is then injected slowly subcutaneously. It is quite important that the heparin be injected into the subcutaneous tissue and not intramuscularly or into the skin. Following the injection the needle is quickly withdrawn and pressure is applied to the site with an alcohol sponge for about 15 seconds to prevent the loss of heparin. If the heparin is *properly* injected into the subcutaneous area there is little likelihood of hematomas, ecchymoses or pain.

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Advantages and Disadvantages

Most of the objections to the use of heparin revolve around its parenteral route. The sublingual route has been advocated for long-time usage,[4] but the effectiveness is debated. Using heparin intramuscularly produces frequent painful hematomas at the site of injection. When given carefully and properly, via the subcutaneous route, pain is not encountered. An occasional slight greenish discoloration of the skin is seen.

The only advantage to the use of coumarins and indanedione derivatives, for the first 30 days, is the oral route of administration. The danger of the coumarins has been repeatedly demonstrated. Difficulty in the regulating of dosage is not uncommon and some patients appear almost impossible to regulate. Prothrombin times are necessary as long as the drugs are taken and there is a real danger of rebound thrombosis should the drug be stopped or control be lost. Control is lost by many factors. (Use of multivitamins *with Vitamin K added,* has recently been an unexpected complication). The broad spectrum antibiotics exert an effect by bacterial suppression of the gastrointestinal tract. Large doses of salicylates have also been observed to exert an anti-K effect and augment the action of the coumarins.

Heparin appears to be a superior anticoagulant.[1] It may well have other advantages for long-term prophylactic use,[2,5,6] such as its plasma clearing ability. Heparin appears to activate a plasma lipase which can reduce the turbidity of postprandial serum. It may possibly act as a coenzyme or as an activator or releasing agent. McDonald[7] has shown that small doses of heparin given to patients with coronary artery disease reverts platelet stickiness, clotting time and thromboplastin generation toward normal. Heparin is also a naturally occurring substance being produced by the body in the mast cells. This is probably why reactions to it have been rare. One aspect of our "safer" feeling regarding the use of heparin is that its effects can be reversed almost immediately with protamine sulfate or hexadiamethrine. At best, several hours are needed to correct the effects of the oral anticoagulants. Occasionally this may not be possible should liver disease supervene (example, hepatitis).

Cost

At present the oral anticoagulants are cheaper. The cost for prothrombin times, however, is a major factor especially in a poorly controlled patient, and this must be added to the cost of the drug. The heparin preparation we use* costs about $30.00 a month, if given once a day on a long-term basis (100 mg./24 hours). In the acute stage given every 12 hours this cost is about $60 for the 30 days of therapy. However, it is not necessary to obtain any clotting times or prothrombin times and this amounts to a considerable saving. In the future this cost to the patient may be reduced when the quantity of heparin used by the hospital is increased. The time saved, in terms of inconvenience to patient and to the physician, is another variable to be considered under cost.

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*Lipo-Hepin®—Riker Laboratories, Inc., North Ridge, California. In the concentrated form of 40,000 U.S.P. Units per cc. (approx. 400 mg. per cc.).

Hazards

Apart from the local complications at the injection sites there are few hazards. Even these local complications will not arise if the drug is administered properly. Rare hypersensitivities to heparin have been reported. Heparin prepared from a different animal source (hog instead of beef) may be necessary, on occasion. Hemorrhage is quite uncommon and its control is immediate and simple.

Comments

The use of heparin during the first 30 days following acute myocardial infarction has been found by us to be a most satisfactory form of anticoagulation. Administered with a small needle via subcutaneous route into the sites described, there is almost no pain and local hematomas are uncommon. Hemorrhage is rare and in addition to the clotting retardation, there is a lipase-stimulating action. There is evidence indicating that heparin retards the atherosclerosis produced by cholesterol in animals.[6] Bleeding times are not prolonged with heparin administration and minor cuts do not cause hemorrhage. The expense during the initial period is no greater than oral anticoagulants when the cost of the daily prothrombin times is also considered.

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MYOCARDIAL INFARCTION IN INFANCY

Myocardial infarction in infancy is most frequently the result of an anomalous origin of the left coronary artery from the pulmonary artery. Twelve cases are reviewed. Emphasis is placed upon the high mortality rate in those cases managed without operation. Evidence is presented which supports the concept that the blood flow in the anomalous left coronary artery is retrograde and that arterial blood is actually drained away from the myocardium into the pulmonary artery. Ligation of the anomalous left coronary artery at its origin combined with revascularization by pericardiectomy and de-epicardialization have been shown to produce encouraging results. Early diagnosis and treatment are mandatory if significant improvement is to be obtained before irreversible changes of myocardial infarction occur.

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ELECTROCARDIOGRAM OF THE MONTH

The Electrocardiogram in Periodic Paralysis

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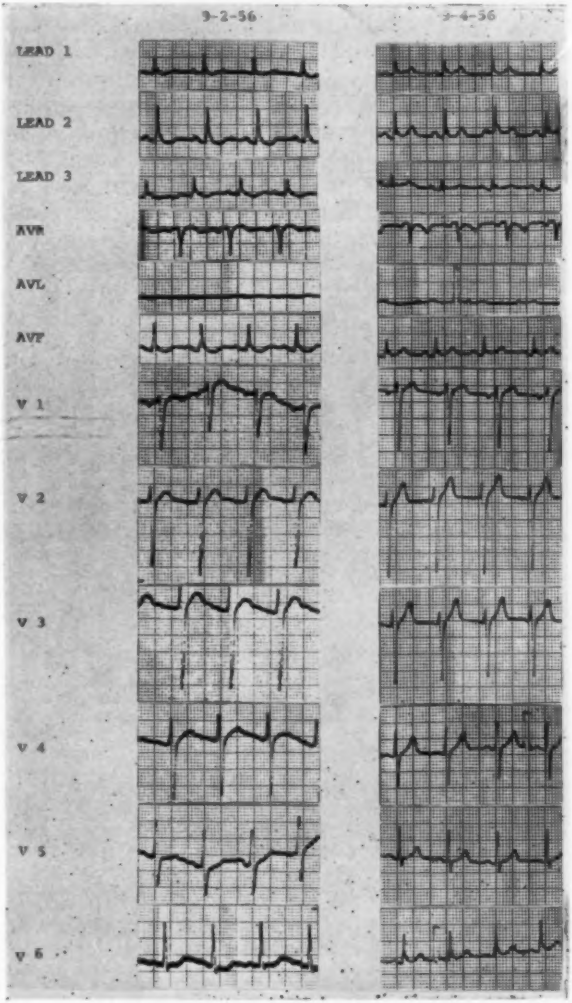
This 31 year-old white male was admitted on September 2, 1956 with a flaccid paralysis of all extremities and trunk for 36 hours. The history was one of recurrent weakness of the legs, first appearing for one day, nine years before, but mostly for the two months prior to admission.



*Instructor in Cliincal Medicine, Tulane University School of Medicine.

During this two-month period he was the manager of an amateur baseball team, and made trips to other towns in the surrounding area. These episodes would occur on lying down or sitting for long intervals, and would last for several hours, remitting spontaneously or, if not full blown, on getting up and exercising. In the week prior to admission, his legs had "given out" several times while walking.

After an initial negative spinal puncture, and in the absence of any familial history, intravenous neostigmine and atropine sulfate were given with moderate return of function of the upper extremities within a few minutes, and slight return of the lower extremities several minutes later. Because of the abnormal initial electrocardiogram and the possibility that this represented hypokalemia, an infusion with 40 m.Eq. of potassium chloride was given the night of admission. The next morning the patient had regained full use of his extremities and has been maintained for four years on oral potassium chloride without a single recurrence.

As he was admitted over a weekend, the full electrolyte profile could not be obtained until two days later, at which time the following startling reports were received—CO_2 21.6 m.Eq./L (normal 22-27), Cl 77.8 m.Eq./L (normal 99-110), K 5.9 m.Eq./L (normal 3.8 - 5-1), Na 114 m.Eq./L (normal 138-146). On this day a repeat electrocardiogram revealed a return to his normal pattern, similar to one taken eight years previously. Another 24 hours of normal nutrition and state of well being, however, resulted in a return of the electrolyte figures to normal.

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We should also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

ROENTGENOGRAPHY OF PERICARDIAL DISEASE

Angiocardiography by delineating the cardiac chambers distinguishes the heart from a surrounding effusion. However, both the right and left heart channels must be visualized to exclude adjacent masses such as mediastinal tumors and pericardial cysts which are usually unilateral. Although the heart is surrounded by fluid in the frontal position in pericardial effusions, in the laferal view the posterior cardiac structures are border forming due to pericardial reflections about the superior and inferior venae cavae and pulmonary veins. Finally, although clinical and electrocardiographic findings should make these instances rare, enlarged hearts due to rheumatic valvular disease (especially tricuspid), and congenital lesions (Ebstein's anomaly, right atrial myxoma and fibroelastosis) may require angiocardiography for differential diagnosis.

Clinical and hemodynamic data are more reliable than roentgenography for the diagnosis of constrictive pericarditis. Angiocardiography will, however, aid in corroborating the diagnosis by establishing widening of the superior vena cava and thickening and stiffening of the pericardium adjacent to the right atrium.

Angiocardiography by showing rotation of the cardiovascular structures is important in the diagnosis of intrapericardial tumors. Another important use for angiocardiography in pericardial disease is for the differentiation of adjacent mediastinal tumors. Finally, angiocardiography by revealing enlargement of cardiac chambers and great vessels establishes the diagnosis of various types of heart disease and excludes involvement of the pericardium.

Steinberg, I.: "Roentgenography of Pericardial Diease," *Am. J. Cardiol.*, 7:33, 1961.

Electrocardiographic Pattern in Acute Pulmonary Embolism Simulating Acute Myocardial Infarction*

A Case Report

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The common electrocardiographic changes in pulmonary embolism have been well documented.[1,2,3] The less obvious electrocardiographic findings include ST segment elevations in the precordial leads. Israel and Goldstein[4] have reported similar observation in leads III and aVF. They also noted some degree of transient ST segment elevation in the right precordial leads in acute pulmonary embolism. In this paper, we present a case of acute pulmonary embolism with ST segment elevation in the precordial leads which closely simulated the changes found in myocardial infarction. Necropsy revealed acute pulmonary embolism with several recent infarctions and there was no evidence of recent or old myocardial infarction despite significant coronary atherosclerosis.

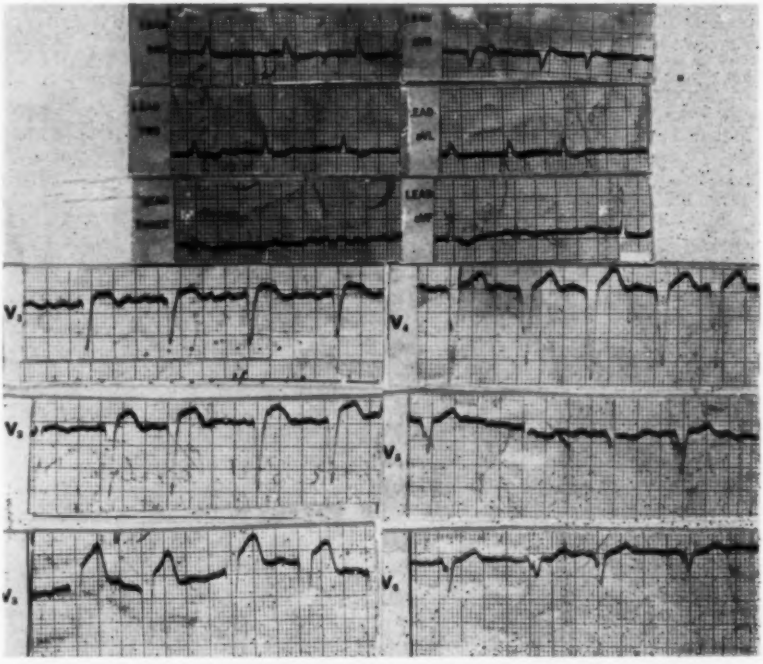

FIGURE 1: Initial electrocardiogram showed atrial fibrillation with deep QS waves in all precordial leads, ST elevations in $V_{1,2,3}$, and varying degrees of intraventricular conduction disturbances.

*From the Department of Medicine, City Hospital at Elmhurst, Department of Hospitals, New York City.

Case Report

A 78 year-old white woman was admitted to City Hospital at Elmhurst on November 19, 1957 because of dyspnea and epigastric pain of ten days duration. There was no history of chest pain or hemoptysis. One year prior to admission, she began to complain of dyspnea and slight ankle edema. Past history revealed rheumatic fever in childhood.

On admission, she appeared alert, cyanotic, dyspneic and acutely ill. The eye grounds showed grade I arteriosclerotic retinopathy. The neck veins were distended There were crepitant rales and dullness over both lung bases.

The heart was enlarged. The point of maximal intensity was in the sixth left intercostal space, outside the midclavicular line. There was atrial fibrillation with ventricular rate of 130 and peripheral pulse rate of 120. Heart sounds were of poor quality and there was a soft systolic apical murmur. P_2 was accentuated. Blood pressure was 110/80.

The liver was enlarged three finger-breadths below the costal margin and the edge was smooth and slightly tender.

The extremities showed a two-plus bilateral pitting edema. Venous pressure was 280 mm. of H_2O.

The initial electrocardiogram taken two months prior to admission (Fig. 1) showed atrial fibrillation with deep QS wave in all precordial leads and ST elevations in $V_{1,2,6}$, and varying degrees of intraventricular conduction disturbances. These findings were interpreted as evidence of an old anterior wall infarction. An electrocardiogram taken during the hospitalization (Fig. 2) showed left axis deviation with rS_1S_3 pattern and deep QS waves in all precordial leads. A third electrocardiogram taken six hours later (Fig. 3) exhibited left axis deviation and marked ST elevations in precordial leads $V_1 - V_4$. Previous deep QS waves in precordial leads V_5 and V_6 have disappeared and were replaced by R waves with ST segment depressions.

Her course in the hospital was characterized by intractable progression despite oxygen, digitalis, mercurial diuretics, anticoagulants and sedatives.

At autopsy, the heart weighed 400 gm., with predominant enlargement of the right chambers and left atrium. The left auricular appendage contained an organized thrombus. The left ventricle was not enlarged. The mitral valve had a fish-mouth orifice. All major coronary vessels showed marked calcific sclerosis with focal narrowing of the lumen, but without occlusion. There was perivascular myocardial fibrosis. Evidence of active rheumatic disease was absent.

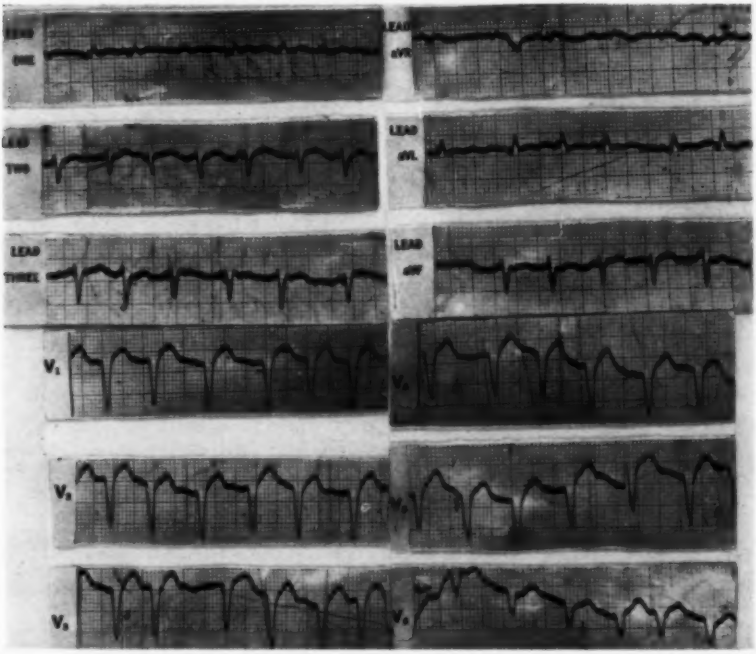

FIGURE 2: Electrocardiogram two months later showed left axis deviation with rS_1S_3 pattern and deep QS waves in all precordial leads.

Both lungs showed organized thrombi occluding the secondary branches of pulmonary arteries, with several fairly large recent infarctions. There were areas of atelectasis scattered throughout the lungs.

Discussion

It has been known for many years that the electrocardiographic pattern of acute coronary insufficiency may be mimicked by pulmonary embolism. In 1949, Dack and associates[7] described ST segment depressions and T wave inversions over precordial leads V_1 to V_6 inclusive, particularly in patients with previous coronary disease.

More recently, Israel and Goldstein[4] observed this pattern in 24 per cent of their cases of pulmonary embolism. They also noted ST segment elevations in right precordial leads in 4 per cent. Transient ST elevations occurred in leads III and aVF, as well as in the precordial leads. The characteristic ST segment elevations in pulmonary embolism are similar to those described in acute coronary insufficiency, in angina pectoris, and after the hypoxemia test.[4-6] It is universally accepted that acute pulmonary embolism may produce subendocardial necrosis of the left ventricle resulting from hypoxia, shock or from pulmonary-coronary reflexes which cause coronary insufficiency.[8] Usually these changes cause a transient ST depression in the right precordial leads. If, however, as in this particular case, previous myocardial changes exist, either as an old myocardial infarction or diffuse myocardial fibrosis, the ST vector may reverse its direction and point toward the damaged area in which case an ST segment elevation will result.

In the case under consideration, the changes in the electrical field occurred simultaneously with the ST segment shift. This was indicated by the appearance of an rS_2S_3 pattern in the standard leads causing the shifting electrical axis to the left (Fig. 2). A second change in the electrical field followed the first one with R waves replacing the previous QS in leads V_5 and V_6 (Fig. 3).

These changes in the electrical field of the heart in conjunction with the ST segment elevations in the right precordial leads must be given serious consideration in the differential diagnosis of acute myocardial infarction and acute pulmonary embolism. In acute myocardial infarction, it is highly unlikely that changes in the electrical field of the heart will occur in one direction to be followed a few hours later

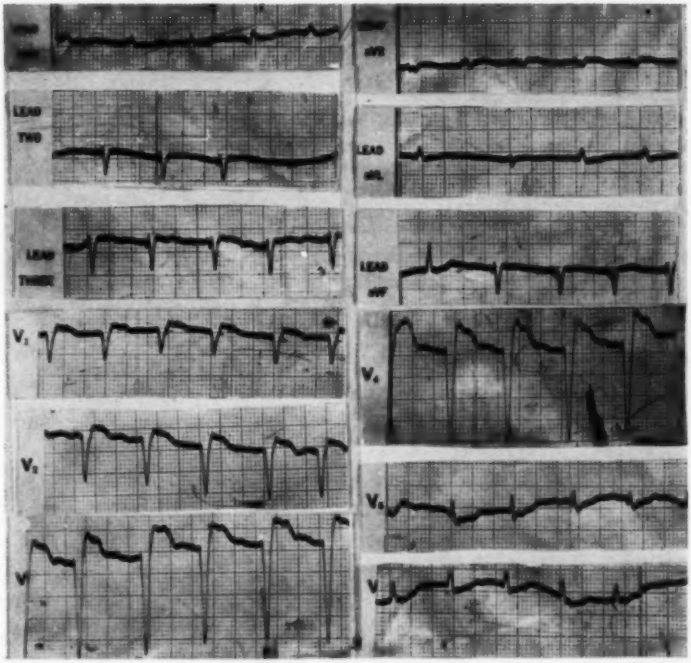

FIGURE 3: Electrocardiogram six hours later showed left axis deviation and marked ST elevation in precordial leads V_1 - V_4 inclusive. Precordial leads V_5 and V_6 showed R waves with ST depression replacing QS pattern with ST elevations seen in Fig. 2.

by changes in the opposite direction. It is plausible to assume that electrocardiographic changes, such as those described in this case, are more prevalent in pulmonary embolism than is commonly realized.

Most investigators are of the opinion that the abnormal changes in the electrocardiogram appear early and disappear rapidly in the course of pulmonary embolism.[9] The onset and duration of the ST segment elevation is not known due to the paucity of published observations. Therefore, early and frequently repeated tracings are desirable in acute pulmonary embolism. In cases of previous myocardial infarction, this is especially important in order to avoid the temptation of diagnosing the condition as a recurrent episode of myocardial infarction.

Figure 1 shows QS waves in all precordial leads and varying degrees of intraventricular conduction disturbances without left axis deviation. The pattern in Figure 2 is in accordance with Grant's description,[10] of left axis deviation with parietal block. However, during the time interval between Figure 1 and Figure 2, the patient was entirely asymptomatic, but the axis change in the electrocardiographic pattern represented by Figure 2 was recorded simultaneously with the development of acute clinical symptoms. Hence, the possibility that Figure 2 represents left axis deviation as a manifestation of acute pulmonary embolism, as well as myocardial fibrosis, cannot be excluded. It is possible that more detailed studies in the form of frequent serial electrocardiographic tracings during the period between Figure 1 and Figure 2 might have given confirmatory evidence in establishing the evolution of these axis changes in concomittance with acute pulmonary embolism.

ACKNOWLEDGEMENT: We are indebted to Drs. Lester Tuchman, Arthur Grishman and James R. Lisa for their advice and encouragement in the preparation of this paper.

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CARDIAC CONTROL

A fundamental feature and, perhaps, a sort of final common pathway of the mammalian cardiac control system is intrinsic myocardial reactivity. On this fundamental feature, neural inhibitory and accelerator influences impinge, the former acting primarily to decrease rate and the latter to increase rate and ventricular reactivity. At low levels of stress, increase in rate is preferred to increased force of contraction. At higher levels, both mechanisms play an integrated role.

Chapman, C. B.: "On the Nature of Cardiac Control" (editorial), *Ann. Int. Med.*, 53:1272, 1960.

Paroxysmal Ventricular Tachycardia*

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The cause of paroxysmal tachycardia has generally been conceived to reside within the heart. Evidence is presented that this may not be true in all instances, and that the central nervous system may be pathogenetically involved.

Paroxysmal ventricular tachycardia occurring in the normal heart is a relatively rare event. Stein and Driscoll,[1] and Lidman and Lyerly,[2] have reported patients without evidence of organic heart disease who developed episodes of paroxysmal ventricular tachycardia. Armbrust and Levine[3] reported that 12 per cent of their patients with paroxysmal ventricular tachycardia had no evidence of heart disease. Lown *et al.*[25] described a syndrome of short P-R interval, normal QRS complex, and paroxysmal supraventricular tachycardia in individuals who were otherwise normal. This triad is apparently related to the Wolff-Parkinson-White Syndrome, yet is distinctly different in that a characteristic delta wave is never present in the electrocardiogram.

Some arrhythmias, including occasional cases of paroxysmal ventricular tachycardia, may be associated with aberrations of the central nervous system. Lucke[12] was the first to report what might be called centrally induced cardiac arrhythmias. He noted persistent auricular extrasystoles in a patient following a head injury. Bernuth *et al.*[4] reported two cases of recurrent "tachycardia" in infants with meningitis and a normal heart at post-mortem examination. Barnes[6] reported a series of cases of paroxysmal tachycardia associated with cerebral manifestations, such as temporary blindness and epileptiform seizures. His case 2 was that of a 34 year-old patient whose typical attack consisted of the sudden onset of dizziness and total blindness for a few seconds, after which the heart suddenly "ran away with itself" in an episode of paroxysmal ventricular tachycardia. In case 4, the attacks of rapid paroxysmal nodal tachycardia were presaged by a sense of pressure in the epigastrium following which the patient became unconscious. Case 5 had paroxysmal tachycardia coincident with epileptiform seizures, blurred vision and hemianopsia. The following case is believed to fall into a similar group of patients, in whom paroxysmal tachycardia may be related in some way to abnormal discharges in the central nervous system.

Case Report

This was the first VA admission of a 41 year-old white man who entered with the chief complaint of "tachycardia." His first attack occurred in 1950, and initially recurred every three to six months, lasting one to two days. In 1956, the recurrences became monthly, therapy consisting of quinidine sulfate 0.2 gm. hourly (24 daily doses) and phenobarbital 30 mg. in the same regimen. Normal sinus rhythm was usually restored in about 48 hours. Prophylactic quinidine was found to be of no value. Recurrences subsequently appeared about every two weeks. In November, 1958, an attack which had lasted for two weeks finally remitted following the intravenous administration of digitalis. While he was confined to the hospital at that time, complete workup including radio-active iodine uptake, was normal. His most recent history is that in the past year the maximum consecutive time he was free of tachycardia

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was one month. In the past six months, the maximum time that he was free of tachycardia was two weeks. In recent months, attacks occurred every week lasting three to four days, that is with a three to four days hiatus during which he had normal rhythm. The attack responsible for his present admission had lasted four weeks. The exhibition of quinidine and phenobarbital hourly for three weeks caused severe gastrointestinal toxicity, with no therapeutic effect. During this attack, as in others of long duration, he noted numbness in scattered areas of the body, and one flight exertional dyspnea. He has never noted pedal edema, orthopnea, paroxysmal nocturnal dyspnea, or nocturia. These attacks usually start with a sensation of "tightening up" in the epigastrium followed in one to two minutes by a "surging of blood" into the head and dizziness without actual syncope. It is then that he would become aware of rapid heart action.

Physical examination revealed a pale, 41 year-old white man in mild acute distress, but not appearing chronically ill. Blood pressure was 92/70 and ventricular rate was 140 and regular. The remainder of the physical examination was within normal limits. Circulation time (sodium succinate) was 23 seconds. Chest x-ray film, complete blood count and BUN were normal. The initial electrocardiogram exhibited paroxysmal tachycardia of an indeterminate type (Fig. 1). He was placed at bed rest, on a salt poor diet, and given digitalis, with no response other than anorexia and nausea probably due to digitalis toxicity. Twenty-four hours later, he noted a period of about 1.5 hours during which he had normal rhythm. Forty-eight hours after digitalization, he again noted a normal rate, and electrocardiogram exhibited regular sinus rhythm, normal QRS, and T wave coving, presumably the "post-tachycardia syndrome." His blood pressure rose to 118/80, A2 was greater than P2, and a short late systolic murmur, grade 1/6, was audible at the apex. He was placed on a maintenance dose (1.5 gm. daily) of procaine amide, but still noted a rapid rate intermittently. However, on one particular occasion he noted that the epigastric sensation which heretofore had always preceded the attacks of tachycardia, was not followed by the tachycardia. The epigastric sensation lasted for about five minutes and then suddenly remitted. Evidently there were two components to his attacks; the first, an epigastric sensation; the second, the tachycardia which was now blocked by procaine amide, which he had never before received. It was then considered that the epigastric sensation might be a manifestation of a temporal lobe seizure. During a subsequent attack, the diagnosis of paroxysmal ventricular tachycardia became evident from the ECG (Fig. 2). An electroencephalogram was interpreted as abnormal, consisting of paroxysmal slowing and occasional spiking in the temporal region bilaterally, but more pronounced on the left side. These abnormalities were increased by hyperventilation. The triad of an aura (epigastric sensation), paroxysmal tachycardia, and abnormal electroencephalogram, suggested a cerebral mechanism for the patient's disorder. At this juncture, the patient was placed on diphenylhydantoin (Dilantin). While on Dilantin, the EEG remained

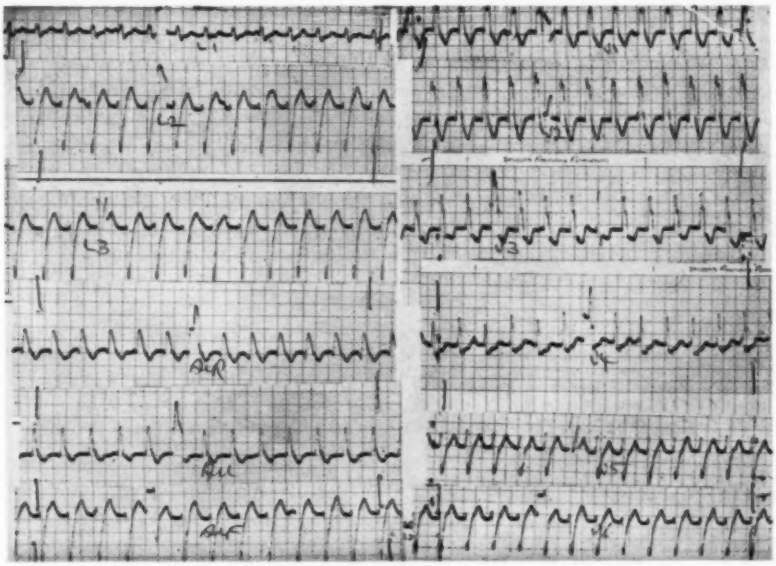

FIGURE 1: Electrocardiogram taken on admission demonstrating rapid tachycardia, either ventricular, or supraventricular with bundle branch block.

unchanged, but the patient had no further attacks for 21 days, the longest attack-free period in over six months. He then "broke-through" with another episode. During his return to normal rhythm, the ECG exhibited further evidence of the ventricular origin of the tachycardia (Fig. 3). Dilantin was discontinued in order that he could receive photic and penthylenetetrazol (Metrazol) stimulation during an EEG. He was, however, placed on procaine amide prophylactically during this period, when he had several additional episodes of epigastric sensation only, not followed by paroxysmal tachycardia. During the photic stimulation, frequent premature ventricular contractions were noted in the ECG; during Metrazol stimulation, a premature ventricular contraction occurred, concomitant with spiking in the EEG (Fig. 4). However, no tachycardia was elicited. Subsequently, he was again placed on Dilantin and remained free of tachycardia for 22 consecutive days. He gradually became refractory to Dilantin, despite dosage to toxic levels, with attacks occurring at more frequent intervals. He was finally placed on maintenance procaine amide and quinidine, which kept him relatively asymptomatic, except for frequent premature ventricular contractions.

Discussion

Penfield[3] promulgated a new concept with his description of a patient with a thalamic tumor who had "epilepsy of the vegetative nervous system." The autonomic phenomena which he described included an increase in pulse rate either during autonomic seizures or by stimulation of epileptigenic foci. Patients with paroxysmal tachycardia not infrequently have some forewarning of an impending episode, just as do some patients with epilepsy. These auras have included a "feeling of fullness, as if I

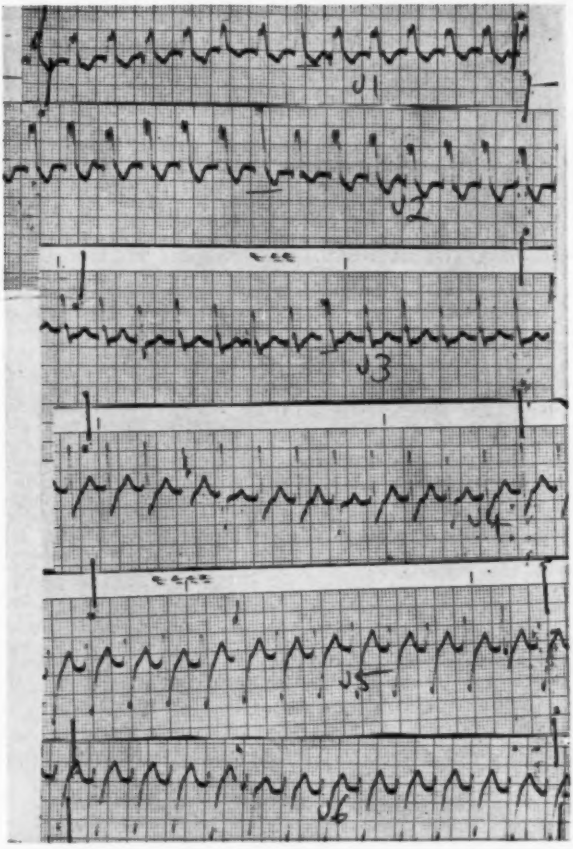

FIGURE 2: Paroxysmal ventricular tachycardia demonstrating ventricular capture beats.

am about to burst," ringing in the ears, fullness in the epigastrium, "gas" in the chest, and "nervous and unwell" in the minutes prior to an attack. According to Penfield and Jasper,[7] visceral phenomena, such as epigastric aura, pounding of the heart, and vasomotor changes may occur as the only manifestations of autonomic seizures. Of interest is that 16 patients in Penfield's series had epigastric and abdominal sensations, or epigastric "rising" sensations, and eight more patients had palpitations as components of their seizures. In those instances in which there was a definite increase in pulse rate, it was considered to be a cardiac aura. In one case, stimulation within the longitudinal fissure produced the typical aura with a "sudden increase" in pulse rate. They described two other cases in whom marked alteration of the pulse rate was noted as the initial phenomenon of the seizures. The authors considered the cardiovascular system to have cortical as well as subcortical representation.

Attempts have been made to demonstrate clinically a relationship between paroxysmal tachycardia and the abnormal EEG. Weinberg[8] apparently was the first to study the relationship between cardiac irregularity and the EEG. In a study of eight patients, he found two to have abnormal EEGs only during the episodes of tachycardia, another with persistently "borderline" EEG, and four (three of whom had prior evidence of heart disease) with persistently normal EEGs. In the former two patients, he did not discount the possibility of secondary cerebral anoxia. It was his conclusion that "EEG abnormality in a case with a history of long-standing paroxysmal arrhythmia without definite evidence of myocardial damage may or may not be pertinent to the cardiac arrhythmia." In relation to EEG changes secondary to cerebral anoxia, a study by Karp *et al.*[10] is worthy of mention. They studied ten normal young men, inducing marked vasodepression, with production of late syncope. They found that only when the mean blood pressure had fallen below 45 mm.Hg. did the EEGs show changes (sporadic low voltage theta waves) and that this occurred shortly before the onset of syncope. They concluded that the central nervous system of normal individuals could withstand hypotension to a remarkable degree.

In 1935, Subbotnik *et al.*[11] published an electroencephalographic study of 16 patients with paroxysmal tachycardia, including one with paroxysms at age 15, following a head injury. It was their experience that attacks were sometimes heralded by "symptoms of general indisposition, anxiety, restlessness and headache." Their patients also described a "shock, blow, stabbing pain in the heart, or a 'wave'," followed by the onset of rapid heart action. Electroencephalograms taken between attacks were abnormal in every instance, resembling those found in migraine and epilepsy, although the abnormalities were less intense than in the latter. Of their 16 patients, 13 showed improvement on Dilantin. Their attacks became less prolonged, occurred at longer intervals, or disappeared altogether. However, three of their patients had no response to Dilantin. In these, EEGs were generally different from those of the patients who responded to the drug. This group of patients responded well to a regimen of caffeine, bromide, and luminal. Indeed, one of these latter patients occasionally experienced a shock in the region of the heart, but no subsequent tachycardia, which had always followed the "shock" in the past. The authors concluded that changes in cortical activity can cause arrhythmias.

For some time, the mechanism of cerebrally-induced cardiac arrhythmias has been investigated by several groups of workers. Brow *et al.*[14] showed that decerebration in cats at the Sherrington level abolished the extrasystoles induced by light chloroform anesthesia. Allen *et al.*[15] were able to prevent the ventricular tachycardia which is precipitated by adrenaline in dogs under cyclopropane anesthesia, by producing a lesion in the pons at the level of the trigeminal nerve. Dikshit[16] found that he could produce cardiac irregularities by injection of acetylcholine, caffeine or nicotine into the lateral ventricles of the brain. The arrhythmias could be abolished by the intravenous administration of sodium barbitone, presumably by its central depressant action, since these effects were present after bilateral vagal section and atropinization. The intravenous dosage of caffeine necessary to produce cardiac irregularity was found to be five times that needed to produce irregularity after local administration into the cerebral ventricular system. Korth *et al.*[27] produced rapid ventricular tachycardia by instillation of strophanthin into the lateral ventricles. The tachycardia could be abolished by intravenous barbital, but not by vagotomy. Froment[17] was able to

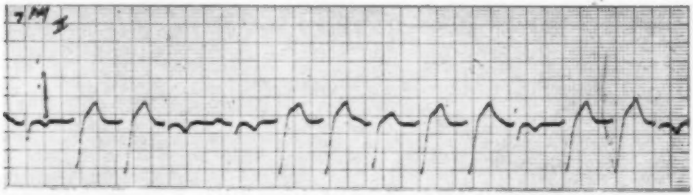

FIGURE 3: Partial recovery from paroxysmal ventricular tachycardia exhibiting frequent ventricular premature systoles, with a short run of paroxysmal ventricular tachycardia.

provoke ventricular tachycardia experimentally by sympathetic stimulation. He suggests that clinically, sympathetic stimulation can be the cause of ventricular arrhythmias in the diseased heart. The stimulation of the posterior or lateral aspects of the hypothalamus itself produces extrasystoles. Weinberg and Fuster[22] were able to elicit in the cat alterations in P, T, and U waves, pacemaker shifts, tachycardia, bradycardia, bigeminy, trigeminy, nodal extrasystoles, escape beats, ventricular extrasystoles, nodal tachycardia and paroxysmal ventricular tachycardia, by stimulation of circumscribed areas in the hypothalamus. Stimulation of a well-circumscribed area in the hypothalamus even provoked QRS configuration of the Wolff-Parkinson-White type. In general, electrical stimulation in the posterior aspect of the hypothalamus resulted in various forms of tachycardia, a "sympathetic" response, whereas stimulation anteriorly provoked a bradycardic response. These observations point to the importance of the sympathetic nervous system in the production of cardiac arrhythmias. Lown *et al.*[23] expressed the belief that the above mentioned syndrome of paroxysmal tachycardia which they had described was due to periodic overactivity of the sympathetic nervous system, possibly originating in the hypothalamus.

Both Brown *et al.*[14] and Dikshit[16] were able to induce extrasystoles by central vagal stimulation. Scherf (1929)[18] demonstrated an indirect vagal action on excitable foci in the ventricles. He found that vagal stimulation in dogs after aconitine administration produced ventricular extrasystoles coincident with the vagal stimulus, the cardiac rate remaining constant. He was also able to produce ventricular tachycardia lasting three to four minutes by vagal stimulation in mammalian hearts which had been previously chemically irritated. Schamroth[19] attempted to elucidate the role of the vagus in cardiac rhythm and arrhythmias by studying the effects of eyeball compression. He was able to induce transient auricular and ventricular tachycardias, and "rebound" sinus tachycardia following eyeball (vagal) release. However, his patients had cardiac disease and many of them were receiving digitalis. Other authors have documented instances of paroxysmal ventricular tachycardia, A-V nodal rhythm, and auricular arrhythmias following vagal stimulation, such as carotid sinus pressure.[20-22] Lennox *et al.*[13] found extrasystoles in 70 per cent of patients undergoing head and neck surgery, and in 40 per cent of patients undergoing other surgery. They concluded that vagal stimulation was responsible. The possible importance of the vagus in the genesis of arrhythmias is evident from the foregoing. The mechanism whereby the vagus might have an effect upon the ventricle was demonstrated by Wedensky.[23] He showed that when an impulse reaches a zone which is partially or completely blocked, the excitability beyond the block is enhanced (*Wedensky facilitation*). In arrhythmias of presumed vagal origin, increased vagal activity occurs, with Wedensky facilitation beyond the blocked zone (possibly the A-V node). It is of interest to note here that Schamroth's patients nearly always had an initial bradycardia before the inception of their tachycardia, auricular or ventricular. If an area beyond the block has been

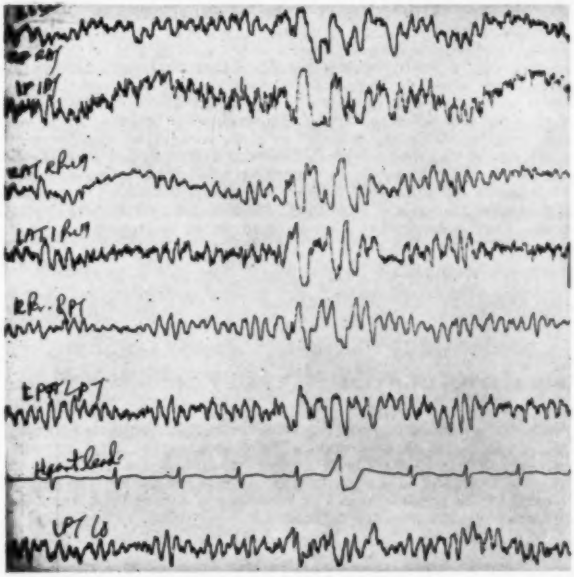

FIGURE 4: EEG and ECG, during Metrazol stimulation. A premature ventricular contraction is noted concomitant with spiking in the EEG.

altered physically or chemically, there may be an increased susceptibility (*Wedensky effect*) to arrhythmias. Hence, a preexisting local abnormality is needed to invoke this mechanism.

In the present case, the neurological mechanism cannot be delineated by the data, other than to suggest that abnormal cerebral activity might be involved in the pathogenesis of the patient's paroxysmal ventricular tachycardia. The data implicated in this conclusion are the patient's "aura" and his abnormal EEG. Although he received only transient relief with the exhibition of Dilantin, his response to therapy is what should have been expected, his EEG being similar to those of Subbotnik's patients who were unresponsive to Dilantin. The use of caffeine and bromide has not been attempted in this patient as he is doing well on the present regimen.

It has been suggested by Gold[24] that Dilantin may have a direct cardiac depressant action. Indeed, Leonard[25] used the drug intravenously along with procaine amide in the treatment of ventricular tachycardia following acute myocardial infarction. Response to treatment occurred only when the Dilantin was added to the regimen. Aguilar[31] used Dilantin in the treatment of extrasystoles and paroxysmal tachycardia with good results. He justified its use on the experimental evidence as noted above, but mentioned no cerebral abnormality in his patients. It has been suggested that other centrally acting drugs may have a direct cardiac action, as well. Burrell *et al.*[26] used hydroxyzine (Atarax) successfully in 30 of 50 patients with arrhythmias including paroxysmal auricular and ventricular tachycardias. Although the authors could not determine the mode of action, they felt that there was a direct myocardial effect, since normal sinus rhythm was attained during the intravenous injection of the drug, or just seconds thereafter. Many of their patients had been pretreated with sedatives, barbiturates and narcotics with no noticeable effect on their abnormal rhythm. None of them had received Dilantin. However, their results do not rule out a primary central action of the drug. It is suggested that lesions of the central nervous system be searched for more frequently in instances of paroxysmal arrhythmia, and that centrally acting drugs be given in therapeutic trial.

ACKNOWLEDGEMENT: The author wishes to thank Dr. Hans H. Hecht for his helpful criticism in the preparation of this manuscript.

All references will appear in reprints.

PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension is a disease of unknown etiology leading to progressive right ventricular failure. Characteristic histologic changes are observed in the small pulmonary arteries and arterioles where subintimal thickening, medial hypertrophy and thrombi cause obstruction of the lumina. Progressive exertional dyspnea, weakness and syncope are the most common symptoms. Anginal type chest pain is frequently encountered. Cyanosis is rare. The picture of right ventricular failure ultimately appears. Physical findings usually noted are a right ventricular heave, an accentuated, closely split second sound, a systolic murmur in the pulmonic area and less frequently a diastolic murmur at the apex or base. The electrocardiogram indicates right ventricular hypertrophy. The chest x-ray confirms the presence of right ventricular enlargement. The main pulmonary vessels are dilated but the peripheral vascular markings are normal or decreased. The lung parenchyma is normal. Diagnosis is confirmed by cardiac catheterization. Characteristic findings are an increase in the pulmonary artery pressure and resistance, a normal wedge pressure, a low cardiac output, and the absence of a shunt. Death usually occurs within five years after the onset of symptoms. The course of the disease is unaltered by treatment which is confined to symptomatic measures.

Langfeld, S. B.: "Primary Pulmonary Hypertension," *Penn. Med. J.*, 64:68, 1961.

ABNORMALITIES OF PULMONARY GAS EXCHANGE IN OBESITY

Pulmonary gas exchange was studied in 20 obese subjects. Some lowering of arterial oxygen tension was present in all subjects, whereas evidence of hypoventilation (arterial CO_2 tension above 48 mm. Hg.) was found in only eight. The suggestion has been made that a disturbed alveolar ventilation-perfusion relationship is a basic abnormality of gas exchange in the obese. Shallow and irregular breathing in a more nearly expiratory position is a possible cause of this disturbed relationship. It is possible that CO_2 retention is a relatively late development in the evolution of respiratory dysfunction due to obesity.

Said, S. I.: "Abnormalities of Pulmonary Gas Exchange in Obesity," *Ann. Int. Med.*, 53:1121, 1960.

Editorial

The Fountain of Trevi of Science

One of the most attractive sights of Rome, Italy, built by the architect, Salvi, in 1735, is the Fountain of Trevi on the via delle Muratte, near the centrally located famous street, the Corso. Its background is an artistically carved façade of a monumental, neoclassical palace. Its statues and bas-relief figures are gazing upon heaps of rocks in the foreground, spouting forth innumerable arching streams of crystal-clear water.

This mental image surged to my mind when I perceived the magnificent gathering of doctors at the Fireside Conferences held at the Hotel Commodore as part of the annual conventions of and jointly sponsored by the American Medical Association and the American College of Chest Physicians.

Truth to tell, on this occasion, the Grand Ballroom of the hotel was the scene of a most unique event in the history of American Medicine. It was unique in scope and technique through the arrangement of direct, personal contact between outstanding experts in various divisions of chest diseases, on the one hand, and practicing physicians anxious to talk with them, on the other hand. It was an event unprecedented in magnitude, bringing together a record-breaking crowd of 1,100 physicians from this country and from abroad.

Throughout its 27 years of existence, medical education has been one of the important endeavors of the polyphasic medical activities of the College. This basic precept has been carried out in the form of postgraduate courses, sponsorship of medical texts, monthly publication of its official journal, medical essay and scientific motion picture contests, regional, national and international meetings and others.

The striking popularity of the Fireside Conferences and their unparalleled success attest to the ingenuity and correctness in their conception, organization and continuance.

Metaphorically speaking, the groups of doctors at the 36 tables set up for these Conferences were like 36 ceaseless fountains exuberantly pouring forth crystal-clear information to all eager to quench their thirst for new knowledge.

The spectrum of coverage was spread over an impressively wide range of subjects. In one sector it was focused on what is new in cardiovascular roentgenology, technical aspects of image amplification, mechanical aids in the diagnosis of heart diseases, etiology of hypertension, stress as a factor in cardiovascular diseases, traumatic heart disease, work evaluation in cardiac diseases, monoamine oxidase inhibitors in cardiovascular diseases, therapeutic use of fibrinolytic agents, modern treatment of congenital malformations of the heart.

Another sector was assigned to pulmonary diseases, such as biopsy procedures, allergic diseases of the respiratory tract, respiratory acidosis, management of emphysema, steroid therapy in lung diseases, occupational diseases of the chest, the lungs in systemic diseases, sarcoidosis,

collagen diseases of the lung, fungus infections, what is the tubercle bacillus, pulmonary cavities, chemotherapy of tuberculosis, treatment of chemotherapy failures, staphylococcus problem, pulmonary embolism and thrombosis, etiology of pulmonary fibrosis, miliary disorders of the lung, present status of IPPB, inhalation therapy.

In the category of miscellaneous subjects, the following were extensively discussed: the cyanotic newborn, pulmonary hypertension, bronchoesophagology, chest trauma, pleural effusions, hiatus hernia.

The basic philosophy of these scientific transactions was to maintain a cooperative approach, informality in discussion and spontaneity in participation. The leit-motif was mutuality. There were no prior rehearsals or instructions. There was no time limit on questions, answers, comments or if you wish to call it, rebuttals. Incredible because of the smooth flow of transactions, there were no rules or regulations, except the self-imposed discipline of respect and deference of good minds.

The nucleus of each group at individual tables was constituted by the moderator and of three to five discussion leaders. These men comprised a galaxy of luminaries of medicine and surgery: experienced teachers, research workers, seasoned clinicians, among them names of known eponyms, from throughout the United States, Canada and Mexico.

In this fashion, a great many matters of pertinence were considered. New drugs were assayed, including their pharmacologic action, dosage, method of administration and possible side effects. Modern diagnostic and therapeutic methods were scrutinized; microbiologic and clinical dilemmas were reviewed. Much critical thought was given to new technical methodology and to setting up standards for everyday practice. Controversial issues were probed with frankness and enlightened objectivity. In addition, there was opportunity for practicing one's diagnostic acumen, alertness and versatility.

Literally, this was a field day for peripatetic possessors of inquisitive minds. They had the privilege of keeping themselves in circulation. They and all of the other participants were invited and encouraged to move from table to table.

It was gratifying to observe that all of the participants were attentive, eager to learn, willing to listen and ready to inquire about further elucidation of puzzling issues.

Questions from participants were dealt with promptly. Of course, in a number of instances, predicated upon variable personal experiences and concepts, the answers of the experts were divergent or sometimes even conflicting. Consequently, there were some animated debates enjoyable to hear. This apparent dissension, however, meant an augmented perspective and served as a provocative stimulant for continued search for better diagnosis and treatment. On the other hand, consensus of the experts carried the hallmark of applicability given by men of wide experience, profound knowledge and prudent judgment.

When auditing the score of these Fireside Conferences, I believe I am correct in saying that in addition to the unquestionably great dissemination of knowledge and occasion for exchange of ideas, these didactic events have had some additional intangible values. As I see it, they must have made a deep impression on all those who had the opportunity to

visit with the magnificent array of great men of our specialty, to watch their minds working and to bask in the brilliance of their intellects.

In summary, the 1961 annual convention and its Fireside Conferences are a matter of medical history. I am certain the Fireside Conferences have accomplished what they were intended to be: prototypes of effective, streamlined medical education which, in their reach, surpassed by far the advantages of colloguiums, panel discussions and open forums. A truly astounding and heartening performance. My humble congratulations and compliments to all concerned.

Now, so as to complete my metaphor fittingly, I wish to cite the legend which says that he who throws a coin in the Fountain of Trevi will be assured of his return to the Eternal City. I am confident, nay, I am convinced that doctors whose registration at the meeting might be symbolic of a coin cast in the Fountain of Trevi, will return to forthcoming Fireside Conferences again and again.

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PULMONARY EOSINOPHILIC GRANULOMA

This particular manifestation of histiocytosis X is seen most often in white males in the younger age group. The symptoms, if any, are usually mild, and cough is a common complaint. A variety of changes are seen on the chest film, but a diffuse, small nodular type of infiltration is the most common. Small cystic areas are also seen. Lung biopsy is the only certain method for diagnosis. The pathologic picture is the same as that seen in eosinophilic granuloma of bone and supports the concept that pulmonary involvement is a manifestation of disseminated histiocytosis X. Sites of extrapulmonary change may be found in the bones and central nervous system. However, from clinical observations, patients presenting with pulmcnary histiocytosis usually do not show evidence of involvement in other organ systems. Pulmonary fibrosis and cystic changes of the lung may result from pulmonary eosinophilic granuloma, and death from cor pulmonale and respiratory failure may occur. However, as judged from the available follow-up information from 45 cases, the lesions tend to regress, and clinical improvement, rather than progression to pulmonary insufficiency, or at least stability, is most often seen; it is not possible to conclude whether any type of therapy (or none at all) hastens regression.

Williams, A. W., Dunnington, W. B., and Berte, S. J.: "Pulmonary Eosinophilic Granuloma: A Clinical and Pathologic Discussion," *Ann. Int. Med.*, 54:30, 1961.

PERICARDITIS: A TEN YEAR SURVEY

Acute nonspecific pericarditis is a relatively common diagnosis and probably represents a group of disease processes. The etiologic agent in many patients is a virus, and in a large group of patients the process is related to a hypersensitivity state or an autoimmune process.

Acute nonspecific pericarditis is not always a benign disease, although in the majority of patients it runs a benign course. Among the complications that may result are pericardial effusion with tamponade, pericardial hemorrhage, acute relapses, the subsequent appearance of chronic constrictive pericarditis, and the occurrence of associated myocarditis.

Adrenal steroid therapy may help dramatically in some patients, but steroid dependence and occasional hypercorticoadrenalism are disturbing complications of this treatment.

Connolly, D. C., and Burchell, H. B.: "Pericarditis: A Ten Year Survey," *Am. J. Cardiol.*, 7:7, 1961.

SCIENTIFIC NEWS ITEMS FROM THE 27th ANNUAL MEETING*

American College of Chest Physicians

ROUND TABLE LUNCHEON DISCUSSIONS

Management of Intractable Heart Failure

Moderator: George C. Griffith, Los Angeles
Panel: George E. Burch, New Orleans
Col. James H. Hammond, MC, USAF, Bergstrom AFB, Texas
William Likoff, Philadelphia
David Scherf, New York City

In the opinion of the panelists, first among the important points in the management of intractable heart failure is reaffirmation of the diagnosis. The next point is determining the cause of the intractability. Is the patient's failure intractable because he is in the end stages of the disease, or is it intractable because ordinary therapeutic measures are not being applied properly, or is it intractable because of failure to consider a more obscure etiology such as beri-beri, anemia, or hyperthyroidism, etc.?

It was the consensus of the members of the panel that in order to avoid treatment errors, the patient should be hospitalized as soon as the diagnosis of intractable heart failure has been established. Some common errors of treatment are: (1) failure of the patient to assume complete rest; (2) failure to adhere to a low sodium diet; (3) over digitalization; (4) improper use of diuretics, causing an electrolyte imbalance which may enhance digitalis toxicity. It was stated that in the case of auricular fibrillation which fails to respond to digitalis, one must think of the possible cause as being hyperthyroidism, WPW syndrome, pulmonary emboli, or reactivation of rheumatic fever.

In the treatment of myocardiopathies, prolonged bed rest of six months to one year or more and the avoidance of high environmental temperatures have produced favorable results. Finally, in intractable heart failure caused by complete heart block, the insertion of an internal pacemaker has frequently proved beneficial.

Management of Resistant Pyogenic Infections of the Lung

Moderator: Chester S. Keefer, Boston
Panel: Joseph E. Geraci, Rochester, Minnesota
Alfred Goldman, St. Louis
Robert I. Wise, Philadelphia

Crucial points of this interesting topic were the subject of a lively discussion at a round table luncheon meeting where it was pointed out that the problem of resistant pyogenic infection of the lung is related not only to the micro-organism concerned, but also to the resistance of the person infected.

Dr. Wise emphasized the extreme importance of early, accurate, bacteriologic diagnosis of the particular infection. He urged the use of an immediate gram-stain smear of the infected material as a guide to choice of antibiotic used. Culture of the material would not only be confirmatory, but also would provide information on antibiotic sensitivity material.

Dr. Goldman reported his experience with prophylactic antibiotic therapy of chronic bronchitis and emphysema, noting that only 30 per cent of his cases benefitted significantly. He urged that such therapy not be used indiscriminately.

Dr. Geraci outlined specific antibiotic therapy of acute infections, particularly the use of vancomycin and dimethoxyphenyl penicillin (Staphcillin) in infections due to penicillin-resistant staphylococcus.

Treatment of Coronary Disease

Moderator: Arthur M. Master, New York City
Panel: Barney M. Dlin, Philadelphia
John J. Sampson, San Francisco
Joseph F. Uricchio, Philadelphia
Arthur M. Vineberg, Montreal

At the request of Dr. Master, the moderator, Dr. Dlin discussed therapy of the emotional aspects of this disease, including sedative therapy, psychologic ventilation, education of the patient, and uncovering hidden fears of the disease.

Dr. Sampson indicated the value of serum enzyme studies to diagnose myocardial infarction and to plan a program of therapy. SGO-T, though specific, declines within 36 hours and requires serial determinations. SGP-T excludes masking acute hepatic disease, except with heart failure. LDH has a delayed prolonged elevation, but is less specific. He suggested long-term anticoagulant therapy for all patients with coronary disease.

Dr. Uricchio commented on possible causal factors in intractable angina pectoris which include infection, anemia, congestive failure, aortic valvular disease and hyperthyroidism. Also, he spoke on therapeutic measures such as bed rest, monoamine oxidase inhibitors, medical thyroidectomy and possibly surgery.

Dr. Vineberg described the technique and rationale of his surgical procedure for the relief of symptomatic coronary disease by epicardiectomy and Ivalon sponge implants. The latter stimulate an unused but inherent ventricular ability to pass muscular blood supply from its lumen via existing arterio-luminal spaces. Ventricular internal mammary artery implants were beneficial and remained patent.

*This is the second group of scientific reports from the 27th Annual Meeting of the College, held at the Hotel Commodore, New York City, June 22-26, 1961. Additional reports will appear in the September issue.

Detection and Management of Drug-Resistant Tuberculosis

Moderator: Raymond F. Corpe, Rome, Georgia

Panel: Howard A. Buechner, New Orleans
J. J. Kirshner, Philadelphia
Henry C. Sweany, Mt. Vernon, Missouri

Dr. Sweany pointed out that historically, the tubercle bacillus had been uniformly considered a stable organism. Natural variants were soon found, but the appearance of specific drugs uncovered an enormous number of previously unsuspected variants. He stated that the desoxyribonucleic acid molecule is composed of four basic simple amino acids, arranged in a number of patterns, combinations and permutations, and that varying complex arrangements account for differences in the various forms of life. These arrangements are alterable as a result of cosmic ray, electrical and other influences. With respect to the tubercle bacillus, emphasis was placed on the need for repeated testing against primary and secondary antimicrobials at various dilutions. He pointed out that **partial** resistance was an expression of the **gradual** destruction of the bacillus by the drugs.

Dr. Buechner addressed himself to the question of the true incidence of primary resistance. He cited the large and growing literature emanating from various parts of the world and noted that the first study, that of the Veterans Administration in 1952, revealed an incidence of 2.5 per cent primary resistance to streptomycin. In 1958 and 1959, in West Africa and Paris, the incidences were 15 per cent and 14 per cent respectively to at least one drug, and 7 per cent to two drugs. He pointed out that the figures will vary with the techniques utilized, that the figures are probably low and that they are rising. These figures were compared with incidences of resistance in retreatment cases where the "primary" resistance is much higher. Retreatment cases represent a serious problem.

Dr. Kirshner explored the problem of prevention of development of resistance. Early treatment, completion of therapeutic regimen and close bacteriologic control are the best current measures. He added that any positive patient should be hospitalized.

Further discussion elicited the fact that the clinician now has a wide variety of antimicrobials for combination usage. Clinicians vary as to their favorites. "Salvage" rates varied from 20 to 40 or 50 per cent. A final hopeful note was struck by Dr. Corpe who stated that with several regimens (including one with streptomycin and pyrazinamide) attenuated every four weeks, definitive arrest should be anticipated in 98 per cent of original treatment cases.

Recent Advances in Inhalation Therapy

Moderator: Edwin R. Levine, Chicago

Panel: Allan Hurst, Denver
James Kieran, Berkeley, California
William F. Miller, Dallas
Joseph F. Tomashefski, Columbus

Following is a summary of the transactions of this luncheon discussion: the primary indication for oxygen therapy is hypoxia. In chronic hypertrophic emphysema, hypoxia should be treated with a gradual daily increase in oxygen concentration in the inspired air up to 40 per cent. Concentrations above 40 per cent should be avoided in the treatment of hypoxia in the newborn premature infant. A simple two-tube test using the comparison of the color of arterial blood before and after equilibration with 100 per cent oxygen and normal venous blood has proved useful for the estimation of degree of unsaturation. Humidification of administered oxygen is essential.

Intermittent positive pressure breathing (IPPB) is indicated where assisted respiration is necessary. It may also be used as an adjunct to aerosol therapy with bronchodilators, although no superiority of this mode of administration over others, using oxygen or a pump as propellants, has been demonstrated.

Bronchodilators by aerosol using a handbulb or a pump or oxygen propelled nebulizer are the most effective method of treatment of bronchospasm. Small freon propelled units dispense large particle aerosols, causing its bronchodilator effects to be produced primarily by systemic absorption from the upper respiratory tract. Their use, therefore, is accompanied by increased systemic side effects of the sympathomimetic drugs administered. Bronchodilators recommended for use in nebulizers are racemic epinephrine, isoproterenol, atropine, phenylephrine and various other sympathomimetic drugs, singly or in combination.

Aerosols of isotonic saline solution heated to 100-125°F. have proved an effective method for promotion of the elimination of tenacious secretions in chronic bronchopulmonary disorders, by virtue of the increased amount of aerosol administered (up to 6 ml. per minute). As a diagnostic method for the recovery of bronchial washings for cytologic study in suspected neoplastic disease of the lung or for bacteriologic investigation for pulmonary tuberculosis, the heated aerosol method, using 10-20 per cent salt solution, is recommended.

Cor Pulmonale

Moderator: Irving Mack, Chicago
Panel: Milton W. Anderson, Rochester, Minnesota
Harry Goldberg, Philadelphia
Thomas W. Mattingly, Washington, D. C.

The moderator, Dr. Mack, called attention to the increased incidence stemming from not only the longer life-span, but also from the effects of thoracic surgery. Defining "cor pulmonale" as "right ventricular hypertrophy due to a disorder of structure or function of the lungs, pulmonary vessels or structures," the definition was qualified by adding a functional division into three etiologic classes: (1) chronic diffuse obstructive emphysema (by far the most common); (2) chronic alveolar hypoventilation; (3) vascular pathology both intra- and extra-luminal. Pathogenetically, he noted factors that increased the right ventricular load through "increased resistance to flow through the pulmonary bed" by: (1) reduction in the bed and its distensibility; (2) vasoconstriction due to hypoxia; (3) increased viscosity of polycythemia; (4) "shunts" in the lung.

Dr. Mattingly remarked that he preferred to think of the overall disorder as paralleling systemic hypertension and so instead of "cor pulmonale," prefers to call it: (1) **pulmonary hypertensive vascular disease** where there are no demonstrable heart changes, and (2) **pulmonary hypertensive cardiovascular disease** where there are heart changes.

Dr. Anderson, though concurring in the opinions expressed, chose to retain the term, "cor pulmonale" not as a disease entity, but as a symptom complex and qualifying it with the proper etiologic term.

Agreeing that right ventricular hypertrophy was of critical diagnostic import, attention was focused on its determination. Dr. Mattingly stressed the difficulty of early recognition, except by the not-too-readily available cardiac catheterization. However, discussed were such clinical signs as "low oxygen reserve," fatigue, limited exercise capacity, and enlargement of right heart (fluoroscopically and by x-ray film) and ECG, systolic precordial lift over right second, third, fourth costal regions; accentuated P_2, serial x-ray films, serial hematocrits. Regarding catheterization results, Dr. Goldberg emphasized that there is "only one hemodynamic factor that means right ventricular hypertrophy and that is a high end diastolic pressure in the right ventricle, namely: above 5 mm. Hg."

Other factors, such as water balance, serum proteins, infections and sudden stresses, were noted and Dr. Mack stated that treatment depended on the cause and that success was contingent upon the reversibility of all or part of the factors.

Management of Bronchial Asthma

Moderator: Howard S. Van Ordstrand, Cleveland
Panel: Giles A. Koelsche, Rochester, Minnesota
George S. McReynolds, Galveston
Leon Unger, Chicago

Dr. Unger pointed out that there are advantages to the new repository method of treatment in bronchial asthma over the conventional method in that the total number of visits is reduced. In new cases of bronchial asthma which are being worked up in his office, he encourages the use of repository therapy. He pointed out that there are disadvantages, with particular reference to constitutional reactions, but stated that when the emulsion is well prepared and is free of the aqueous component, patients do not develop constitutional or severe reaction. In his opinion, the patients derive as much benefit from the repository type of therapy as they do from the aqueous therapy.

Dr. Koelsche discussed the hospital control of severe bronchial asthma and status asthmaticus and pointed out the following necessary protocol for the management of such patients: (1) there has to be an environmental control of the patient; (2) the patient must receive a measurable degree of rest and reassurance that he is going to get well, plus whatever therapy in the nature of drugs are indicated at this time; (3) the efforts must be directed toward liquefaction of thick, inspissated mucus; (4) there must be adequate control of cough; (5) there must be a control of the patient's hypoxia.

Dr. McReynolds stated he felt that infection of the paranasal sinuses was an important cause of a great many cases of bronchial asthma. In cases in which he observed minimal bronchiectasis, he felt that the reservoir infection in the sinuses should be corrected. He said that maxillary sinus infections were of importance in the causation of bronchial asthma. He found that in the management of such cases, irrigation of the sinuses was quite helpful and that in some instances, a modified Caldwell lock operation is of decided benefit. He related that men in his field are now using balloons in the treatment of maxillary sinus infections, inserting the balloon into the sinus and filling it with oil; the subsequent compression of the mucous membrane of the sinus is helpful in bringing the infection under some element of control. It was his opinion that when the maxillary sinus is cleared up, other sinuses usually subsequently clear up themselves. He observed that the cases of minimal bronchiectasis may lead to intractable asthma unless some therapy is utilized. He emphasized that stock vaccine and autogenous vaccines are of little or no value in such cases.

Dr. Van Ordstrand commented on the middle lobe syndrome with minimal bronchiectatic changes in the asthmatic patient and said that these are bound to persist in spite of therapy and in spite of allergic management.

Dr. Unger expressed the opinion that approximately 75 to 80 per cent of asthmatics needed some form of hyposensitization therapy. Dr. Koelsche was of the opinion that 50 per cent or perhaps less than 50 per cent of bronchial asthmatics needed desensitization.

General discussion which followed brought out the necessity of removing foci of infection in all patients with bronchial asthma. Relative to the use of steroids in bronchial asthma, it was the consensus of the panel that steroids are useful when used intelligently. It was felt by the panel that bronchoscopy could be a lifesaving measure and should be employed whenever necessary, especially if thick inspissated mucus failed to be expectorated by the patient. There was an adequate warning, however, that certain of the procaine derivatives used in topical anesthesia prior to bronchoscopy have to be considered, and that there was a definite risk and, in some instances, subsequent death caused by anesthetic methods prior to bronchscopy. The use of antibiotics in infections in bronchial asthma was discussed by the panel and the important point was raised and agreed upon by most of the panel, namely that chloramphenicol is an excellent antibiotic in bronchial asthma, but it must be used with definite caution.

Unsolved Problems in Prevention and Treatment of Tuberculosis (Open Forum)

The main concern of this panel, moderated by Karl H. Pfuetze, Chicago, was how new cases of infection can be prevented. It appeared to Edith Lincoln, New York City, that tuberculin testing of infants and children and treatment of positive reactors are the fundamental problems since it is these that form a reservoir of future cases of active tuberculosis. In this connection, Dr. Lincoln posed the question of treatment of the adolescent positive reactor and as the discussion developed, the participants of the panel felt that recent convertors at all ages should be treated with INH for six months to a year. W. Leonard Howard, Northville, Michigan, stressed the necessity of retaining the hospitalized patient until the sputum becomes negative and indicated that in this respect a broad rehabilitation program consisting of patient education, diversional therapy and social service to the family is essential. Compulsory isolation of recalcitrant patients should be enforced. Edward T. Blomquist, Washington, D. C., pointed out that in the community, in contrast to the hospital, less than 5 per cent are recalcitrant patients and suggested that this group does not constitute an important public health menace. He indicated that more facilities should be made available for follow-up care of those not hospitalized. Finally, Sidney Dressler, Denver, discussed the role of "anonymous" acid-fast organisms in infection. He seemed to feel that more adequate initial treatment of active cases of tuberculosis might increase the present 90 per cent conversion of sputum and thus reduce the residual number of potential positive-sputum cases.

SCIENTIFIC REPORTERS

The following members of the College were invited by the Editorial Board to serve as scientific reporters at the various sessions of the 27th Annual Meeting, held in New York City, June 22-26:

Vincent J. Adams, Forest Hills, N. Y.
Irene Anday, Chicago, Illinois
Herbert S. Anhalt, Roslyn Heights, N. Y.
Gustav J. Beck, New York City
Irvin R. Besman, New Hyde Park, N. Y.
A. J. Conte, New York City
Francis Coughlin, Jr., Stamford, Conn.
Thomas DeCecio, Cliffside Park, N. J.
Mary Allen Engle, New York City
Charles Fadem, Lakewood, New Jersey
Oscar Feinsilver, Worcester, Mass.
Ira Gelb, New Rochelle, New York
Seymour L. Halpern, New York City
Abraham Jezer, New York City
Carol Kramer, Atlantic City, N. J.
Irving Kroop, Brooklyn, New York
Milton I. Levine, New York City
Monte Malach, Brooklyn, New York
Armond V. Mascia, Tarrytown, N. Y.
Jesse Minnis, Brooklyn, New York
K. G. S. Nair, Norwalk, Conn.
H. Allan Novack, Boston, Mass.
Benjamin Potter, Jersey City, N. J.
Edward H. Robitzek, Staten Island, N. Y.
Isadore Rosenfeld, New York City
Irving Sarot, New York City
Nathan Silbert, Lynn, Mass.
John Vance, Buffalo, New York
John C. Weaver, Bronx, New York
Walter Wichern, New York City
Roger H. L. Wilson, San Francisco, Calif.

Officers and distinguished guests of the College seated on the dais at the Annual Convocation, Sunday, June 25, Hotel Commodore, New York City. Dr. M. Jay Flipse, Miami, President, is at the rostrum.

1961 ANNUAL MEETING DRAWS RECORD ATTENDANCE

New York City, host for the 27th Annual Meeting of the College, attracted a record attendance of more than 2,200 members and guests, the highest registration ever attained at a national meeting. The scientific program was hailed as one of the best in the history of the College. An outstanding display of 34 technical exhibits attracted the interest of the attending physicians.

Seminars, Administrative and Committee Meetings

The meeting opened on Thursday, June 22, at the Commodore Hotel, with Postgraduate Seminars on cardiology and pulmonary diseases, both medical and surgical. On Friday, June 23, examinations for Fellowship in the College were held during the morning, and concurrently, two open forums were presented, one on "Unsolved Problems in the Prevention and Treatment of Tuberculosis" and another entitled "The Chest Conference Approach to the Teaching of Diseases of the Chest." The Board of Regents held its annual meeting on Friday morning and the joint luncheon meeting of the Governors and Regents of the College was held at noon, followed by the open administrative session. During the afternoon, the annual meetings of the 52 councils and committees of the College were held, which were attended by more than 500 members. The New York State Chapter held a meeting on Friday evening where Dr. Herman E. Hilleboe, Commissioner of Health for the State of New York, was guest speaker. Dr. Hilleboe presented the Eleventh Annual Howard Lilienthal Lecture; his presentation was titled "Tuberculosis in a Changing World." He was introduced by Dr. Andrew L. Banyai, Director of International Affairs of the College.

Scientific Assembly

On Saturday morning, June 24, the scientific program opened with a highly successful "Cine Symposium," an innovation which was received with tremendous interest and enthusiasm. The Cine Symposium was arranged under the direction of the Committee on Motion Pictures of the College. It is anticipated that this very successful part of the program will be repeated in 1962. The scientific program continued through Saturday and Sunday, June 24 and 25, in two concurrent assemblies, one devoted to cardiovascular diseases and the other to pulmonary diseases. In addition, there was a motion picture program presented simultaneously with the scientific program on Saturday afternoon and all day Sunday, where recent films on diseases of the chest were shown. Round table luncheon discussions on many aspects in the treatment of heart and lung diseases were held on Friday, Saturday and Sunday, June 23, 24 and 25, as well as on Monday, June 26, as a part of the joint session of the College with the American Medical Association.

The scientific program presented on Monday, June 26, at the New York Coliseum, sponsored by the Section on Diseases of the Chest of the AMA and the American College of Chest Physicians, drew the attention of more than 1,500 physicians. The joint section meetings on Tuesday and Wednesday, June 27 and 28, also attracted large crowds.

Convocation

The Annual Presidents' Banquet of the College was held on Sunday night, June 25, and was preceded by the Annual Convocation and cocktail party. Guest speaker at the Convocation was Judge Warren E. Burger, United States Court of Appeals, Washington, D. C., who gave the Sixth Annual Louis Mark Lecture. The title of the lecture was "The Doctor in Court." Honorary Fellowship in the College was awarded to Rear Admiral Edward C. Kenney, Surgeon General of the U. S. Navy; Dr. Luther L. Terry, Surgeon General of the U. S. Public Health Service; and to Dr. Edward A. Boyden, Research Professor of Anatomy at the University of Washington. Dr. Dean B. Cole, Richmond, and Dr. Edgar Mayer, New York City, were awarded certificates of Honorary Regent in recognition of their many years of service to the College in that capacity. Dr. Seymour M. Farber, San Francisco, immediate past-president of the College, was presented with the certificate of Master of the American College of Chest Physicians. Dr. Hollis E. Johnson, Nashville, incoming President, addressed the new Fellows of the College. Fellowship Certificates were presented to 194 new members of the College at the ceremony.

Annual Presidents' Banquet

Awards

More than six hundred members of the College and their families and guests attended the Presidents' Banquet. A number of awards were made on this occasion, including the presentation of the College medal to Dr. Alvan L. Barach, New York City, for meritorious achievement in disease of the chest. Dr. M. Jay Flipse, Miami, President of the College, awarded the medal and also presented the 1961 essay awards. The first prize and $500.00 went to Dr. Leonard Pisnoy, who had just received his doctor's degree from the University of Buffalo, for his essay titled "Studies on the Pulmonary Vascular Resistance." Second prize certificates and $300.00 were won by Malcolm I. Jayson, Ephraim D. Bennett and David Rubenstein of Middlesex Hospital Medical School, London, for their joint essay on "The Perception of Dyspnea." Mr. Alan Williams, British Consul General in New York City, was present to receive the certificates for

the British authors. Third prize winner, Dr. James N. Burkeholder, who had just received his degree from the University of Missouri, was present to receive his certificate and $200.00. An honorable mention certificate and $50.00 prize were won by Domingo Martinez Gutierrez and Salvador Morales Mendez of the Faculty of Medicine of Seville, Spain.

Awards for the best films presented in the Annual Motion Picture Program were awarded by Dr. Paul H. Holinger, Chicago, chairman of the Committee on Motion Pictures. First prize was presented to Dr. Edwin R. Levine, Chicago, for his film entitled "Hypoxia—Indications for Oxygen Therapy," and honorable mention certificates were awarded to Dr. Marco Bruschi, Bakersfield, California, for his film on "Coccidioidomycosis;" to Drs. Dwight E. Harken, Warren J. Taylor and Samuel A. Levine, Boston, for their film entitled "Valvuloplasty for Mitral Stenosis;" and to Drs. Franklin R. Smith and Edward A. Boyden, Seattle, for their motion picture on "Surgical Anatomy of the Pulmonary Hylum: Part I."

ANNUAL COLLEGE FILM AWARD

Dr. Paul H. Holinger (right), Chicago, chairman, Committee on Motion Pictures, presenting first prize certificate to Dr. Edwin R. Levine (center), Chicago, for the outstanding medical motion picture presented at the College meeting. Mr. Allan Claghorn (left) represents the Linde Company, Division of Union Carbide Corporation, sponsor of the film.

In Appreciation

Dr. Seymour M. Farber, immediate past-president of the College, awarded the Presidential Scroll to Dr. Flipse and the College pin to Mrs. Flipse. The new President, Dr. Hollis E. Johnson, Nashville, was introduced and a bouquet of roses was presented to Mrs. Johnson. Mrs. Henry J. Heimlich, chairman of the ladies committee, was presented with a bouquet of roses and an expression of appreciation was extended to her and to the members of her committee for the splendid program of activities planned for the ladies.

Dr. Flipse expressed the appreciation of the officers and members of the College to Drs. John F. Briggs, St. Paul, Howard S. Van Ordstrand, Cleveland, and Coleman B. Rabin, New York City, for the organization of an excellent scientific program, and to Dr. Paul H. Holinger, Chicago, and his Committee on Motion Pictures, for the organization of the Cine Symposium and the Motion Picture Program. A vote of thanks was extended to the chairmen and members of the New York Chapter committees for their part in making the meeting so successful.

The banquet was followed by the annual dance, sponsored by the New York State Chapter of the College. A "Champagne Hour" was presented by the Arthur Murray Dancers, which was most entertaining.

Fireside Conferences

On Monday, June 26, the Fireside Conferences were held at the Commodore Hotel as a joint presentation of the College and the American Medical Association. There were 36 round tables in the Grand Ballroom, each containing a panel of experts on a selected subject. Approximately one thousand physicians were in attendance during the evening, starting shortly after 8:00 p.m. and continuing until 11:00 p.m.

Scientific Exhibits

Two special exhibits sponsored jointly by the Section on Diseases of the Chest of the American Medical Association and the American College of Chest Physicians attracted a great deal of interest at the New York Coliseum. The Special Exhibit on Pulmonary Function, which has been shown at AMA meetings for the past eight years, is sponsored by the Committee on Pulmonary Physiology of the College, under the chairmanship of Dr. Joseph F. Tomashefski, Columbus. Dr. George R. Meneely, Nashville, is chairman of the exhibit committee and directs its program.

The Special Exhibit on Physiologic Testing of Cardiac Function was presented for the first time in New York City, sponsored jointly by the Section on Diseases of the Chest of the American Medical Association and the Committee on Cardiovascular Physiology of the American College of Chest Physicians. Dr. John S. La Due, New York City, is chairman of the College committee. Dr. Rudolph E. Fremont, Brooklyn, chairman of the exhibit committee, directed the production of the exhibit. It is planned to re-organize the exhibit for its showing in 1962.

Several of the exhibits in the Section on Diseases of the Chest received awards, as follows: Certificate of Merit to Drs. Lyle H. Hamilton, Josef R. Smith and Ross C. Kory, Veterans Hospital, Wood, Wisconsin for the exhibit entitled "Use of Gas Chromatography in the Evaluation of Pulmonary Function;" Certificate of Merit to Drs. O. W. Kincaid, G. D. Davis, H. J. C. Swan, W. H. Weidman and A. H. Bulbulian, Mayo Clinic and Mayo Foundation, Rochester, Minnesota for the exhibit on "Selective Angiocardiography in the Diagnosis of Congenital Heart Disease;" and Honorable Mention was awarded to Drs. Richard F. McLaughlin Jr., Walter S. Tyler, Donald W. Edwards, Robert O. Canada, Gerald L. Crenshaw, Murray A. Fowler and Edward A. Parker, U. S. Naval Hospital, Oakland, and University of California School of Veterinary Medicine, Davis, California, for their exhibit on "The Experimental Production of Emphysema in the Horse."

COMMENTS FROM COLLEGE MEMBERS

We acknowledge the following communications received at the College office in Chicago with reference to the annual meeting held in New York City this year:

July 7, 1961

"My heartiest congratulations to you for the fantastic and excellent job done for the College meeting held here in New York. There were large crowds, inordinate interest, and remarkable organization at this meeting. I need not go further in telling you how much the various talks, panels and fireside conferences were enjoyed."

Arthur M. Master, M.D.
New York City

28 June 1961

"I should like to comment on the administrative handling of the recent meeting and convocation of the College of Chest Physicians in New York from which I have just returned. In the numerous meetings which I have attended during the past several years I have observed none in which the flow of events proceeded with such smoothness and good organization. You are certainly to be highly commended upon the excellence of the arrangements and the College is most fortunate in having such an able Executive Director."

George A. Higgins, Jr., M.D.
Washington, D. C.

July 7, 1961

"As one who belongs to many societies—too many, perhaps!—I want to congratulate you on the splendid arrangements you and your staff made for the meeting of the American College of Chest Physicians recently concluded.

"Never have I attended a large meting of this size where everything ran so smoothly. I thought you might like to have this reaction from one of your most recent Fellows."

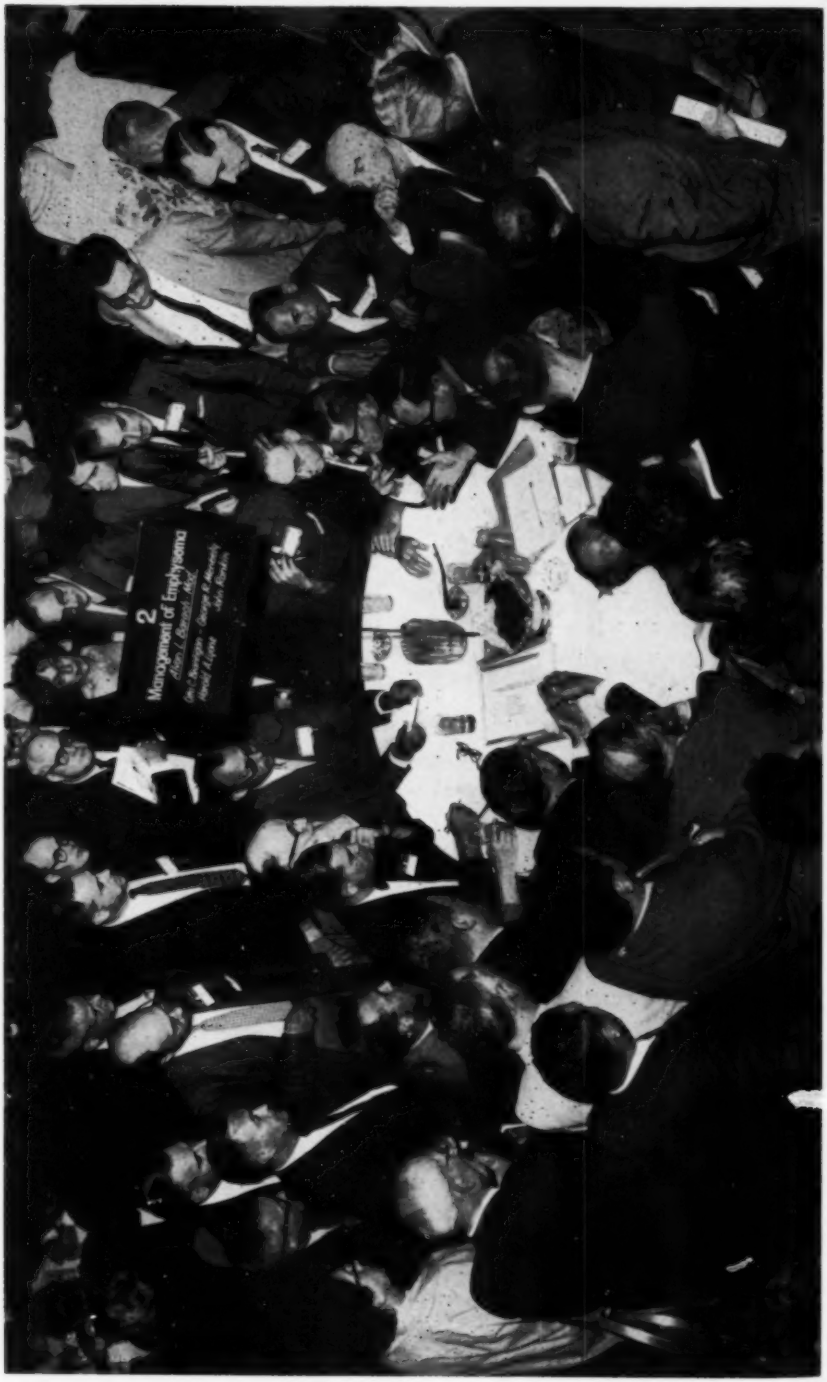
M. Coleman Harris, M.D.
San Francisco, California

CHANGE IN COLLEGE BYLAWS VOTED ON AT ANNUAL MEETING

A change in the College bylaws was approved by the membership at the annual administrative session in New York City, June 23, to the following effect:

"The Governor of the College in each state in which a chapter of the College exists, as well as the Regent of the College in the district, shall serve as ex-officio members of the Executive Committee of their respective state chapters and shall receive notification in writing of all meetings of the Executive Committee of their respective state chapters."

College chapter officials, and particularly the secretaries, whose duties include notification of Executive Committee meetings, are requested to make note of the above addition to the bylaws.



FIRESIDE CONFERENCES, COMMODORE HOTEL, NEW YORK CITY, JUNE 26, 1961

A typical science fair—"peripatetic learning." The Fireside Conferences were sponsored jointly by the American Medical Association and the American College of Chest Physicians.

ADMINISTRATIVE SESSIONS

The Board of Regents and the Board of Governors of the College held their annual meetings in New York City on June 23. A number of council and committee reports were reviewed by the Board of Regents, some of which were approved for publication and some referred back to committee for re-evaluation. The following report of the Treasurer was approved by the Board of Regents.

Report of the Treasurer

Statement of Income and Expenses
for the Year Ended December 31, 1960

INCOME:		
Annual Dues—U. S. and Canada	$138,353.75	
Annual Dues—Other Countries	17,930.34	$156,284.09
Fellowship Fees		24,634.26
Sales—		
Advertising	$ 53,062.37	
Subscriptions	30,142.82	
Miscellaneous	3,267.23	
	$ 86,472.42	
Less—Discounts Allowed	10,503.27	75,969.15
Exhibit Space		11,606.99
Miscellaneous		9,885.63
Interest Received on U. S. Savings Bonds, Treasury Notes and Bills		1,241.88
Interest on Investment and in Savings & Loan Associations		2,637.53
TOTAL INCOME		$282,259.53
EXPENSES:		
Salaries—Administrative Staff	$ 79,300.00	
Salary—Director of Education and Research	6,666.56	
Payroll Taxes	1,695.00	
Journal, Diseases of the Chest—		
Printing	54,018.37	
Postage and Shipping	7,544.78	
Envelopes	1,131.00	
Editorial Board	5,037.50	
Engraving	1,313.53	
Translations	300.00	
Office Expense—		
Printing	6,287.16	
Supplies	3,157.27	
Telephone and Telegraph	4,168.73	
Postage and Shipping	5,358.88	
Public Health Counselor	35.11	
Officers and Committees	5,017.68	
Meetings—		
Annual	10,967.62	
Semi-Annual	2,736.31	
International Congress	7,417.55	
Travel—		
Executive Director	1,403.30	
Director of Education and Research	2,222.88	
Membership Certificates	745.15	
Library	419.69	
Public Relations	2,185.69	
Contribution to National Society of Medical Research	25.00	
Awards—		
College Medal	87.90	
Essays	1,205.38	
Audit	400.00	
Employees Retirement Fund	3,373.56	
College Building Operation	12,095.27	
Total Expenses		226,316.97
NET INCOME		$ 55,942.56

Ralph H. Marcus
Certified Public Accountant
Chicago, Illinois

Albert H. Andrews
Treasurer

Elections

The following elections were held at the meetings of the Board of Regents and Board of Governors.

Dr. Edward H. Morgan, Seattle, elected to the Committee on Nominations by the Board of Regents.

Dr. Howard S. Van Ordstrand, Cleveland, elected to the Executive Council by the Board of Regents.

Dr. J. Arthur Myers, Minneapolis, and Dr. Andrew L. Banyai, Chicago, re-elected members of the Editorial Board by the Board of Regents.

Dr. Arthur M. Olsen, Rochester, Minnesota, re-elected chairman of the Board of Regents.

Dr. Irving Willner, Newark, re-elected vice-chairman of the Board of Regents.

Dr. Henry R. Hoskins, San Antonio, elected to the Committee on Nominations by the Board of Governors.

Dr. Howell S. Randolph, Phoenix, re-elected chairman of the Board of Governors.

Resolutions

The following resolutions were adopted by the Board of Regents:

(1) WHEREAS, a number of sanatoriums for treatment of the tuberculous have closed and others are contemplating closing, and

WHEREAS, trained personnel engaged in the treatment of tuberculosis for many years find it necessary to obtain employment in other fields of medicine, and

WHEREAS, the services of these trained workers in the field of tuberculosis could be profitably utilized in countries where tuberculosis is still endemic, and

WHEREAS, many of the physicians and other trained personnel have expressed a desire to continue work in their chosen field in other countries,

THEREFORE BE IT RESOLVED, that plans be developed by the American College of Chest Physicians for the employment of such personnel in countries in need of their services, and

BE IT FURTHER RESOLVED, that the financing of this project be discussed with the proper departments in our Government, the World Health Organization, foundations, and other interested parties.

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(2) WHEREAS, conflicts in dates and duplication of projects have occurred because of the increase in the various activities undertaken by College chapters throughout the country, and

WHEREAS, these conflicts have a direct bearing on the success of the projects,

THEREFORE BE IT RESOLVED, that any activity, such as a postgraduate course, an essay contest, a special scientific study, etc., be submitted to the appropriate council or committee of the College for approval before definite action is taken by the chapter.

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(3) WHEREAS, a publication of the College entitled **"The Hospital Counselor"** was changed to **"The Public Health Counselor"** in order to cover a broader field, and

WHEREAS, at the present time **"The Public Health Counselor"** is under the jurisdiction of the Council on Hospitals of the College,

THEREFORE BE IT RESOLVED, that **"The Public Health Counselor"** be transferred to the Council on Public Health of the College, and published under its jurisdiction.

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(4) WHEREAS, no provision has been made for mature physicians from other countries desiring to further their medical education by observing the methods of teaching in the United States, and

WHEREAS, the American College of Chest Physicians desires to assist such physicians,

THEREFORE BE IT RESOLVED, that yearly scholarships not to exceed $500.00 each be established for a three-year period to assist such educational endeavors, and

BE IT FURTHER RESOLVED, that the candidate must be a member of good standing in the American College of Chest Physicians in his country and that he be recommended by his Regent and Governor for application to the Committee on Resident Fellowships, and

BE IT FURTHER RESOLVED, that $2,000.00 per annum from the general funds of the College be allocated for this purpose.

The following resolution was adopted by the Executive Council and Board of Regents of the College, June 22 and 23, 1961, and adopted by the College membership at the open administrative meeting, June 23, 1961, New York City.

WHEREAS, the American College of Chest Physicians is interested in the best medical care for all the people, including our aged citizens, and

WHEREAS, it is the belief of the members of the American College of Chest Physicians that the King bill HR 4222 would result in poorer rather than better medical care for the aged, and

WHEREAS, it is the belief of the members of the American College of Chest Physicians that the King bill is a step in the direction of socialized medicine, which is not in the best interests of our people, and

WHEREAS, the Congress has already passed the Kerr Mills bill which would adequately take care of aged individuals who need medical services,

THEREFORE BE IT RESOLVED, that the American College of Chest Physicians express its opposition to the King bill HR 4222 and any similar measures which will lead to inferior medical care.

PLANS FOR 1962 ANNUAL SCIENTIFIC PROGRAM ANNOUNCED

Plans for the scientific program to be presented at the 28th Annual Meeting of the College in Chicago, June 21-25, 1962, are under way. Physicians interested in presenting papers are invited to submit a 200-word abstract to the Committee on Scientific Program for consideration. Abstracts may be forwarded directly to the program chairman, Dr. Joseph W. Peabody, Jr., 1150 Connecticut Avenue, N.W., Washington, D. C.

The Committee on Motion Pictures is interested in learning about new films on diseases of the chest for possible presentation at the 1962 annual meeting. Please send all pertinent information regarding new films to Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois. Those accepted for presentation at the 28th Annual Meeting of the College will be eligible for the 1962 Film Contest and will be referred to the judging committee for review. The deadline for submittal of films for the motion picture program is **January 1, 1962.**

COMMITTEE ON NOMINATIONS

Members of the Committee on Nominations for offices to be elected in 1962 are:

Dr. Edward H. Morgan, Seattle, Chairman
Elected by the Board of Regents

Dr. Henry R. Hoskins, San Antonio
Elected by the Board of Governors

Dr. Francis G. Kravec, Youngstown
Appointed by the President

Recommendations for elective offices may be addressed to Dr. Edward H. Morgan, 1118 Ninth Avenue, Seattle, Washington. The committee will meet during the interim session of the College in Denver, November 25-26.

Election of officers for 1962-1963 will be held at the 28th Annual Meeting of the College in Chicago, June 21-25, 1962.

CHAPTER NEWS

Kentucky Chapter

The Kentucky Chapter will hold its annual meeting in Louisville, September 19, in a combined session with the Kentucky Roentgenological Society, during the annual meeting of the state medical association. The program, which will begin at 2:00 p.m., is as follows:

Basic Chest Diagnosis from an Internist's Standpoint
Virgil A. Plessinger, Cincinnati

Basic Roentgen Signs in Chest Diagnosis
Jerome F. Wiot, Cincinnati

Panel Discussion: "Chest Lesions" and selected case reviews

Moderator: David Shapiro, Louisville

Panel: John S. Harter, Louisville
Virgil A. Plessinger, Cincinnati
Jerome F. Wiot, Cincinnati